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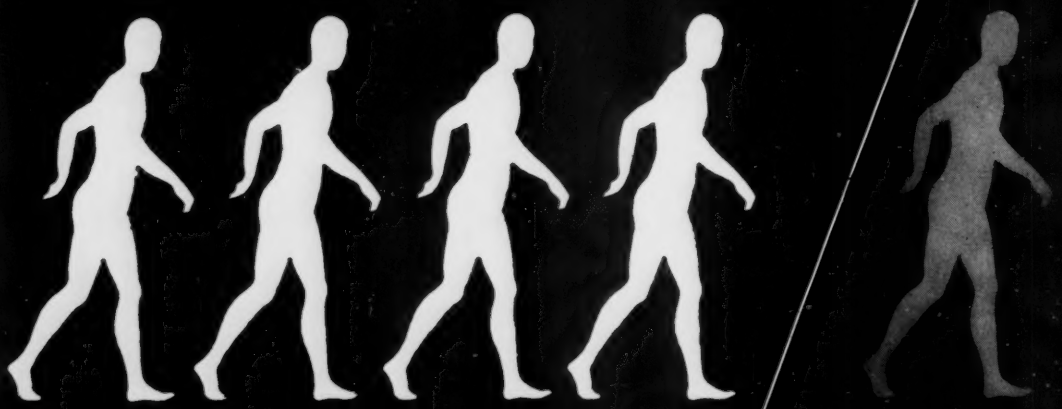

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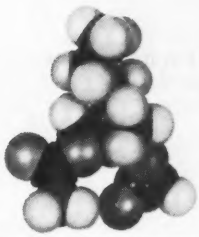

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Editorials

TUBERCULOSIS AND CHEMOTHERAPY

A Critical Review of New Developments

DURING the past few decades our thinking about tuberculosis has undergone changes which have influenced clinical practice, just as some clinical practices, which came upon us with overwhelming and almost empirical force, have changed our thinking about the tuberculous process. The most powerful of these has been specific chemotherapy. However, its success and its impact on the antituberculous effort could not be what it is had it not been preceded by equally important although less publicized developments. After one of the greatest triumphs in public health had been achieved in this country by the almost complete elimination of bovine tuberculous infection through government-sponsored control of the milk supply, the fight against the disease during the past 25 years has been decisively influenced by several other developments.

The first of these was the end of what might be termed the climatic era in phthisiotherapy. The migration of tuberculous patients to climatically favored parts of the country, generally to the west and southwest, began to cease when it was realized that the disease could be cured just as well in or near the home area, that a better climate does not close tuberculous cavities, and that by this migration the patient often traded sunshine, cleaner air, and mountain views against medical skill and equipment. We now realize that, instead of the tuberculous patient, we should have sent and still should send the nontuberculous patients suffering from chronic sinusitis, bronchitis, and some forms of asthma and bronchiectasis. The main force in abandoning the climatic therapy, however, has been the complete or partial assumption of financial responsibility for the care of the tuberculous by local and state governments in many parts of the country. In the State of New York, for example, every patient is able to pursue his cure and convalescence free from worry about the cost of medical care. All physicians who from earlier years remember the mental anguish caused by financial worries which threatened to annihilate and indeed often did annihilate our medical efforts through months and years of institutional treatment, appreciate the relaxation with which physician and patient can now go about planning the best course to be followed.

Another great development came with the recognition of two negative factors, namely, that really early tuberculosis most frequently leaves the patient without noticeable symptoms and that much pulmonary disease cannot be discovered by physical examination. Certainly small pulmonary infiltrates defy the most skillful

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From the Division of Pulmonary Diseases, Montefiore Hospital, New York.

Presented at the Annual Meeting of the New York State Chapter of the American College of Chest Physicians, New York, February, 1955.

percussion, auscultation, and palpation; but extensive and even spectacularly advanced disease frequently escapes attention. The failure of physical examination to discover early pulmonary tuberculosis and, consequently, the futility of undertaking early diagnosis campaigns based on that method is now recognized by all.

The diagnostic problem began to be solved with the increasing use of the roentgen ray, first as an accessory to physical examination and more recently as the mainstay of our efforts in the examination of the chest. The slogan now for about two decades has been that tuberculosis has to be seen, not heard, and public health agencies have focused their propaganda for early diagnosis by x-ray examination by changing from the "symptoms are danger signals" technique to the "don't wait until you feel sick" method.

Those of us who belong to the older generation look back, not with regret, but with some nostalgia, to the days when the skill in physical examination, a keen eye and a sharp ear, made a good diagnostician. Nowadays, the only percussion sound heard in physicians' offices along Fifth Avenue comes from the bands marching by in a parade.

It has been this turn in our diagnostic experience which made us ready for the effective use of chemotherapy, since it has its most decisive and lasting effect on the early and symptomless exudative infiltrate. Chemotherapy has come to the fore not as a recently initiated effort but rather as the culmination of many years of search which became successful in the wake of the development of general chemotherapy. A study of the history of tuberculosis reveals that after Robert Koch's discovery of the bacillus in 1882 the chemotherapy of the disease was his first concern. It is interesting, and was good for our knowledge of tuberculosis, that his chemotherapeutic researches led him to the discovery of the fundamental facts about specific tuberculous hypersensitivity and acquired immunity. Eight years after the discovery of the bacillus, in 1890, he made the following statement *:

In the course of time I have tested a very large number of substances for their influence on tubercle bacilli in pure culture and it was found that not a few substances are able to inhibit the growth of tubercle bacilli in very small doses. Of course, more cannot be expected of a drug. It is not necessary, as often has been assumed erroneously, that the bacteria be killed within the body. It is sufficient to inhibit their growth and multiplication in order to render them innocuous for the body. As agents which in very small doses prove to inhibit growth, to mention only the most important we recognize a number of etheric oils, the aromatic compounds B-naphthylamin, para-toluidin, and xylidin. Some so-called tar dyes as fuchsin, gentian violet, methylin blue, chinolin yellow, anilin yellow, and auramin; among the metals mercury in steam, and silver and gold compounds, especially the cyangold compounds, were noted for their superior effect over all other substances. In a dilution of 1 to 2 million they diminish growth of tubercle bacilli. All these substances remain completely ineffective when they are tried in tuberculous animals. In spite of this failure, I was not deterred from the search for growth-inhibiting agents and eventually have found some which not only in the test tube, but also in the animal body can inhibit the growth of tubercle bacilli. My experiments are not completed and I can say about them only that much, that guinea pigs which are known to be exceedingly susceptible to tuberculosis will not react to a vaccination with the tuberculous virus after they have been exposed to the influence of such a substance and that in guinea pigs which already are ill with a very high degree of generalized tuberculosis the disease process can be arrested completely without the body being unfavorably influenced by the substance. From these experiments I can

* Reference 1. This article has been translated and previously published by me in Transactions of the 47th Annual Meeting of the National Tuberculosis Association, Cincinnati, Ohio, 1951, p. 465.

make no further conclusions at present but that the possibility heretofore rightly doubted, namely to render pathogenic bacteria innocuous in the living body without doing it any harm, has thereby been proved."

In two subsequent articles † Koch described in greater detail what has since been termed Koch's phenomenon and finally states that the "agent" (*mittel*) with which the new cure of tuberculosis was being practiced was a glycerin extract from pure culture of tubercle bacilli. Later during the same year Koch published another paper entitled, "Further Communication on the Tuberculin."[4] This is the first mention he makes of that name, establishing his drift from attempts with true chemotherapy into the immunology of tuberculosis.

On the basis of Koch's work investigators in pathology established the main lines of our present knowledge of the manifold tuberculous processes and were able to lead the way out of the errors of Virchow's theory of the duality of phthisis and the nonspecificity of consumption and tuberculosis. Contemporary students in their most recent studies of the pathology of tuberculosis have reported important new observations of the tissue changes under the influence of antituberculous drugs. Auerbach[5] reports that the essential tissue response as compared with the spontaneous healing of tuberculous lesions is the inhibition of the perifocal exudative reaction, preventing to a large extent the productive changes which used to be found during the prechemotherapeutic era. Similar findings recently were published by Pagel and Simmonds.[6] These investigators observed the open healing of tuberculous cavities, which appeared well epithelialized without residuals of tuberculous tissue changes. Although the occasional occurrence of such findings cannot be doubted, it would be premature and dangerous to advocate the assumption that annular translucencies in the roentgen picture represent reliably innocuous excavations when repeated or even frequent sputum tests fail to reveal tubercle bacilli.

It is of paramount importance to clarify the role of chemotherapy in the healing of cavernous tuberculosis. The cavity, next to the initial tubercle itself, is by far the most important pathological unit in pulmonary tuberculosis. It is the source of redistribution of bacilli to the patient himself and to the outside world. As long as a cavity can be demonstrated roentgenologically, it is—to repeat this warning—a precarious undertaking to consider tuberculosis as healed or arrested, regardless of how favorable the clinical and pathological disease picture may appear otherwise. For some time to come, it will be wise for clinicians to remain cautious about the open healing of cavities as a result of chemotherapy. Clinical experience has shown that old fibroid disease and the excavations which it subsequently contains are influenced only little or not at all and that whatever effect the drugs may have in this type of tuberculosis is one on the bacillus rather than on the existing pathological picture. There is good reason to doubt the decisive effect of drugs, not only on the old well-walled cavity but even on the freshly developed excavation in exudative caseous disease. The processes of deflation of overinflated defects or their inspissation with necrotic material, or both, was a common observation in prechemotherapeutic times if the patient's respiratory effort was reduced by profound bed rest; at best they are only hastened by drug therapy, but it is not a rare occurrence nowadays to see cavities unresponsive to chemotherapy and even to see them enlarge, although the nonexcavated lesions in

† References 2 and 3.

the same lung improve or disappear. The all-important favorable cavity behavior therefore cannot be listed hastily as one of the results of chemotherapy. There is a possibility that Auerbach's [7] findings of the inhibition of tissue response at the bronchocavitary junction can prevent what we may term clinical-pathological healing by inspissation, contraction, and lasting closure of the caseous tuberculoma, which in small cavities can be followed by sufficient calcium deposition to insure irreversible healing.

There are no convincing findings that chemotherapy inhibits the further development of already arrived necrosis by interrupting the multiplication of bacilli, but it does seem to change the consistency of necrotic material. Our own observations on resected specimens have shown a much greater frequency of thin, fluid pus within cavernous lesions after drug therapy than used to be seen in untreated tuberculosis, where necrotic material of a firmer and truly caseous consistency prevailed. This, together with an open bronchial communication, could enhance the possibility of bronchogenic distribution if virulent bacilli have persisted. Cavernous tuberculosis benefits from chemotherapy indirectly through the tremendously enhanced use of thoracic surgery, especially by resection, which has become safe only by means of preoperative and postoperative coverage with antibiotics. Next to the therapeutic triumphs with miliary and meningeal tuberculosis, this so far has been the greatest definite achievement of the drugs.

More controversial than the effect of antibiotics on tuberculous tissue is at this time the response of the tubercle bacillus itself. A strong claim ‡ has been made that it is killed within closed caseous lesions from which it cannot be cultured, although it may be seen in abundance on microscopic examination. This would make much of the resectional therapy unnecessary, because the danger of redistribution from the caseous tuberculoma would be removed. A number of recent investigations,§ including one of our own, so far have failed to support these findings, and a therapeutic program relying on them could bear tragic results. Even if all the organisms contained in a lesion failed to grow, we do not know whether we are dealing with a bactericidal or merely a bacteriostatic effect which may fade. Not nearly enough experience has been garnered, not nearly enough time has elapsed since the first findings became available, to enable us to pass judgment on this almost literally explosive matter.

It is with uneasy feelings that we discharge patients in whom we know of or suspect persistence of cavitation, although the sputum may be negative in institutional tests. It is necessary in these cases and justified in all discharged patients to safeguard against reconversion of the sputum and its sequels by continuation of drug therapy over a long period of time, not months but years and perhaps indefinitely. The first trials with such a program [11] are promising.

The difficult question of the infectiousness of tuberculosis has become more complicated rather than simplified by chemotherapy. On one hand is the new factor of the dissemination of new disease by bacilli which have become resistent to the drugs; on the other is the decline of primary inoculation of the population; it has raised our concern about the decreasing protection by a good immunity acquired at an early age, which is still our best safeguard against tuberculous

‡ D'Esopo, N.; Bernstein, S.; Decker, A. M.; Raleigh, J. W., and Steenken, W.: Bacteriology of Lesions Resected During Chemotherapy, Ref. 8, p. 229. Steenken, W.: Methods of Determining the Viability of Tubercle Bacilli, Ref. 8, p. 268.

§ References 9 and 10.

disease. One does not need to see catastrophe in the moderate distribution of bacilli by occasional contacts with our neighbors. Many years ago the eminent English investigator Louis Cobbett [12] wrote against the excessive protectiveness toward children:

> It would appear that great care must be taken lest things be made worse instead of better; for if this immunization by means of small doses of widely distributed bacilli is playing any important part in increasing the resistance of the present generation, it is just possible that by checking the distribution of the bacilli, as for example by discouraging indiscriminate spitting, we may actually be undermining the resistance of the race, and paving the way for a future increase in the severity of the disease, and it was unfortunate that so much importance was attributed to the danger of infection by means of tubercular sputum dried and pulverized and distributed in the streets and public places in the form of dust, since it has tended to foster the idea that everybody is continually being exposed to infection which may set up grave disease in the more susceptible. The quantity of such bacilli inhaled at any one time must be, one would think, as a rule exceedingly small, and not improbably harmless to ordinary people, or possibly even protective.

Today, more than ever, it seems unlikely that disease is spread by a little infected sputum on a subway platform or by eating from a plate served by a tuberculous waiter. The available figures show that tuberculous disease essentially originates from the daily intimate contact with the openly tuberculous in work and particularly in home life, mostly without the recipient of infection being aware of its presence. Three times as much clinically important tuberculosis has been found among persons known to have been exposed to such contact than among any groups of the general population, including the socially underprivileged.[13] We are now worried about absence of specific sensitivity and, consequently, immunity among young people and resort to the artificial incorporation of bacilli by BCG vaccination. Since the strength and duration of the protection which it affords are still unknown factors, we cannot hope to have replaced much of the spontaneously acquired protection which preceding generations have enjoyed. We know that whole populations not previously exposed have been decimated by acute epidemics of tuberculosis after the disease had been imported to them. It is not possible that, with the increasing lack of acquired immunity, we could have a similar experience in times of stress. Perhaps we could look upon it as an "act of providence" that just at the time when the fight against protective infection is threatening to become too successful we are provided with chemotherapy, the greatest strength of which is that it curbs the acute forms of tuberculosis. The greatest blessing of drug therapy may yet prove to be that it can enable us to receive the spontaneous inoculation with the organism which leads to our protection by the development of a good immune resistance with much less danger of the development of progressive clinical disease.

There is much talk these days about the impending eradication of tuberculosis, which has become the slogan on the banner of some organizations. According to Webster's Dictionary, "to eradicate" means "to pluck up something by the roots." The root of tuberculosis, in spite of the tremendous importance of social, economic, and emotional influences, is and will remain the tubercle bacillus, and there is no hope that we will ever eradicate that ubiquitous little organism from the face of the earth or even from this country. Of all of our internal enemies who have an affinity for red, it will be the last one to stop its subversive activities. Referring again to Webster's Dictionary, we find that "to control" means "to exercise a restraining or directing influence, to regulate, hence to hold from action, to curb."

Isn't this a sounder and more truthful definition of what we ought to do and, in fact, of what we have been trying to do through all these years? Since we are never going to eradicate the tubercle bacillus and, therefore, will never eradicate tuberculosis, we should drop that term and modestly and truthfully return to the concept of control of tuberculosis, which we conceive of as reducing the disease to moderate proportions.

We have become rather smug about the tuberculosis problem; already before the advent of chemotherapy we viewed with too much satisfaction the decline of the mortality rate which appears to have been precipitous in this and other countries since the arrival of the drugs. It does not detract from the proud record of achievement to point out that the decline has not been as great as could be assumed from the published statistics. By improved methods of therapy we have learned to prolong life over many more years than used to be the case. The patient who was found to have tuberculosis in 1900 and who died in 1902 would have a fair chance to live to 1965 or even 1975 if he had been born 50 years later and became tuberculous in 1955. But it does not mean that eventually he will not succumb to the disease. This is expressed in the age statistics of tuberculous patients, which show that the highest number of deaths now occurs between the ages of 50 and 70, whereas it used to be found between the ages of 20 to 30, a few decades ago. It is an unpleasant truth to state that we are keeping alive sources of infection which used to be taken by death during the era of climatic therapy. Our hospitals are filled with middle-aged and elderly patients with more extensive disease, with more complications, in greater need of a variety of medical procedures, and with greater social and emotional problems, than we have ever had before. In other words, with a greater need for institutional care.

So far, the discussion has concerned itself with some of the pathological, bacteriological, and statistical aspects of chemotherapy and their implications. How great their importance will be remains to be seen. All that can be said now is that differences from older observations are being studied and recognized but that no revolution has occurred in our thinking about the behavior of the tuberculosis process. Scientifically, one of the greatest gifts of chemotherapy has been not so much the earnest discussion of a thousand different schemes and procedures of antimicrobial treatment as the furthering of basic research in tuberculosis, which was badly in need of stimulation.

On the clinical side, a real upheaval has occurred in the general management of the tuberculous patient; under the influence of widespread and consistent, in part irresponsible, publicity in newspapers and magazines, overoptimism about the possibilities of chemotherapy has seized the public and to a large extent the medical profession. In the field of tuberculosis, where pathologists and bacteriologists sometimes turn clinicians overnight, the old doctor is bewildered by the demand that almost everything he believed in and practiced through the years be thrown through the door so magically opened by the miracle drugs. Is he just outdated, clinging to old-fashioned ideas? After all, he does realize that a new era has arrived, that pneumothorax and other collapse methods have outlived their usefulness, and he has discarded these methods to a large extent. Why should he oppose the other new concept, so frequently defended nowadays, that institutional treatment for tuberculosis can be replaced by therapy at home, and why deplore the closing of tuberculosis hospitals? We remember how much money has been spent by the organizations fighting tuberculosis to bring their arguments

for institutional therapy to the reluctant patient. To cite some authorities and examine the validity of those arguments today, Chadwick and Pope,[14] in their book "The Modern Attack on Tuberculosis" wrote

> Experience is the best teacher and living a sanatorium life is a personal experience that makes the patient aware of his handicap and the necessity of keeping within the limits of the safety zone defined by his disease. Rest, both mental and physical, is the keystone upon which recovery is built. This is the first lesson that a patient has to learn. To promote healing, the diseased lung must be put as completely at rest as possible and kept so as long as the disease is active. The patient upon admission becomes an individual with a broken body and disturbed mind and not just a pair of lungs sent in for repairs. The sanatorium is a place where patients' lives are carefully regulated. The rest periods are not interrupted as they would be at home by well-meaning but ill-advised friends. The X-ray equipment needed to record the course of the disease and as a guide in treatment is always at hand.

The experience that the behavior of the fresh tuberculous cavity is more the result of respiratory exertion or rest than of the influence of chemotherapy is a powerful argument against abandoning expertly organized bed rest and relaxation, and, in addition, it seems that all of the points made by the authors remain valid.

Perkins and Feldmann, in their guide for tuberculous patients,[15] published only three years ago, advise

> The doctor is sure to prescribe one basic, simple treatment that is essential and universal in the treatment of tuberculosis. It is rest. Not even a new "miracle" drug, however active it may be against the germ causing tuberculosis, can exert its full effect without this accompanying basic treatment, rest. So your doctor will tell you to go to bed in a tuberculosis hospital and stay there—not for a few days, not for weeks, but perhaps for months.

So far, the scientific and clinical experience with chemotherapy does not warrant any deviation from this counsel.

Against the fanciful writings of newspaper columnists stands squarely the statement of the Committee on Therapy of the American Trudeau Society[16] in June, 1954:

> The Committee again states that, from the facts available, there is no evidence to support a reduction in the amount of rest therapy from that of past practices except as this may be justified by an earlier attainment of an inactive status of the disease. There appears to be no doubt that antimicrobial therapy has materially shortened the period of recovery in the average case of tuberculosis, and that it has greatly decreased the case mortality rate. This does not necessarily imply, however, that it has altered the indications for rest therapy during the active phases of illness. The indications for rest therapy during the active phases of tuberculosis are not altered by the proposals that patients may subsequently be treated with either surgical collapse or resection.

Nobody except the fearful patient and his shocked family will claim that rest and relaxation can be provided even in the best home as they are in a hospital. Official experimental programs with home treatment without the benefit of initial institutional care seem to comprise largely patients who inadvisedly have refused to enter a hospital or sanatorium; in other words, a virtue is being made of the necessity to apply at least a minimum of medical help. Home care in the majority of these cases is synonymous with clinic attendance, since the patient has to leave his home for almost all the essential diagnostic and follow-up procedures. However, there should be no objection to ambulatory care which aims to be not a substitution for but rather a well-organized addition to hospitalization. The latter may well be shortened by successful chemotherapy, especially in early and minimal cases of the disease. With the observation of all necessary safeguards, such as investiga-

tion of the suitability of the home and of the social conditions of the family, such plans have been reported as giving satisfactory initial results.[17]

There also has been a considerable increase of home treatment without preceding hospitalization by private physicians, and the seeming panaceas of chemotherapy has lured many patients to stay under the care of general practitioners, some of whom are insufficiently experienced in the diagnosis and treatment of pulmonary diseases. It is distressing to admit patients with hopelessly advanced bronchogenic carcinoma to the hospital after they have been kept home under antimicrobial therapy in the assumption that their disease is tuberculosis.

It has been argued by some that there is no scientific proof of the benefit of bed rest in tuberculosis. While it is impossible to obtain scientific proof in the full sense of the word, we do have evidence of clinical experience with patients who did well under hospital care and whose disease became reactivated after their return home, only to improve again after they reentered an institution. No more convincing evidence could be asked for.

To a large public one of the most impressive demonstrations of the seemingly decreasing need for institutional treatment has been the closure of tuberculosis sanatoria, especially of some with a glorious past and reputation. Few seem to realize that country sanatoria far from the city are not forced to close because chemotherapy has made them superfluous but rather because they have increasingly lost their usefulness with the end of the climatic era of the therapy of tuberculosis. This development has been in the making since well before the drugs arrived, when it was realized that the modern treatment of the disease should best be placed within the framework of general hospitals, where not only the best opinions and equipment for medical and surgical procedures and for complications are available but which also offer the opportunity to teach tuberculosis in comparison with the other pulmonary diseases and to stimulate much needed research among medical students and young physicians. The only country institutions for a city population which could endure through complete service with the best standards are the few located in the immediate proximity of urban areas and operated as integral parts of general hospitals.

The time since the beginning of effective chemotherapy has been brief. We are using drugs almost empirically, without knowledge of the mechanisms by which they operate. Eight years of experience with a treatment are a very short period to predict the final results in a disease which often takes decades to cure or kill. It seems appropriate to close these remarks by paraphrasing a paragraph from Fishberg's book on pulmonary tuberculosis, published 36 years ago[18]:

> It seems that the pessimism as to the value of antituberculous drugs displayed at present is mainly due to the fact that too much was expected from them. They are no panaceas for phthisis. Some enthusiasts have in fact promised too much and when at present these drugs do not come up to the extravagant expectations of some, they are altogether condemned. This is as unjust as the extreme enthusiasm of those who claimed that the drugs will solve the tuberculosis problem.

Actually, Fishberg wrote this paragraph about tuberculosis sanatoria, to dampen the extreme enthusiasm and exaggerated expectations which prevailed about sanatorium treatment in his time. The only change which I made was to replace the word "sanatorium" by "drugs." If one considers our present ignorance about the permanent effect of drugs on the micro-organism and the tissues, the uncertainty about the development and behavior of drug resistance, and the restrictive effect of chemotherapy in the general management of the disease by laxity with hospitaliza-

tion and exclusive reliance on so-called home care, it is possible and even likely that the paraphrased version just quoted will become a depressing reality.

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Kidney Biopsy

A Review of One Hundred Successful Needle Biopsies

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In evaluating a new procedure such as needle biopsy of the kidney, it is important to know (1) its ease of performance, (2) its morbidity and mortality, and (3) its clinical usefulness. The first two points have been covered fairly well previously by us and by others.* In order to assess the last point we have chosen 100 successful renal biopsies and compared the clinical and pathological impressions. These 100 biopsies are taken from a total of 169 biopsy attempts, of which 131 yielded renal tissue. In 31 patients, however, the results were discarded from the study because the biopsies were unsatisfactory or because they were repeat biopsies on the same patients.

METHODS

Kidney biopsy specimens were obtained by means of a Turkel needle, formalin fixed, paraffin embedded, sectioned, and stained with hematoxylin and eosin and whatever other stains were necessary.[5] Such sections measured 5 to 20 mm. in length and 1 mm. across and consist mostly of cortex containing 10 to 40 glomeruli. Renal biopsies were considered adequate only if at least 10 glomeruli were present. From these sections an adequate idea may be obtained of the condition of the glomeruli, convoluted tubules, loop of Henle, interstitial tissue, arterioles, and the small arteries of the cortex. Clinical diagnoses were arrived at by carefully evaluating the history, physical examination, and laboratory data, including in each patient the examination of the urinary sediment on several occasions. The urine was examined in the following manner. A 15 ml. specimen was centrifuged; the supernatant fluid was discarded, and a drop of the sediment was placed in the center and at each end of a microscope slide. To one drop of sediment Sternheimer's stain[10] was added; to one drop, Sudan 3 stain[11] was added, and cover glasses were placed on each of the three drops. The unstained specimen was examined for red cells, red cell casts, types of nucleated cells, and casts and was examined with polarized light for fat. The preparation stained with the Sternheimer stain was utilized to identify more exactly the types of nucleated cells, the types of casts and the presence or absence of "glitter" cells. The Sudan-3-stained preparation was used to further identify fat in cells or casts.

For practical clinical purposes, without other things to suggest a more unusual diagnosis, the following diseases were usually considered in the clinical diagnosis of renal disease: acute and chronic glomerulonephritis, pyelonephritis, arteriolonephrosclerosis, malignant nephrosclerosis, hemoglobinuric nephrosis, and diabetic glomerulosclerosis. Interpretation of the findings in the urinary sediment was based on the criteria as shown by Lippman.[12] In addition, the presence of "glitter cells" in the sediment was considered highly suggestive of pyelonephritis.[10]

RESULTS

Of the 100 patients so studied a correct diagnosis was made clinically in 39 instances. The pathologist was able to arrive at a definitive diagnosis in 91, and in 9 no diagnosis was made. A breakdown of the results for the diseases listed previously is presented in Table 1. As can be seen, acute glomerulonephritis was most readily diagnosed on clinical grounds. The incidence of correct clinical diagnosis was lowest in malignant hypertension, nephrosclerosis, and diabetic glomerulosclerosis. The greatest clinical error occurred in making a diagnosis of chronic glomerulonephritis or diabetic glomerulosclerosis when on biopsy the patients were found to have arteriolonephrosclerosis. In those instances thought to be chronic glomerulonephritis this occurred in patients who

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TABLE 1.—*Summary of Results*

	Diagnosed Clinically	Correct	% Correct	Diagnosed Pathologically	Missed Clinically	% Missed Clinically
Normal	3	3	100	10	7	67
Acute glomerulonephritis	18	16	89	20	4	20
Chronic glomerulonephritis	25	10	40	15	5	33
Pyelonephritis	10	6	60	10	4	40
Nephrosclerosis	6	4	50	24	20	90
Malignant nephrosclerosis	1	0	0	3	3	100
Hemaglobinuric nephrosis	2	2	100	4	2	50
Diabetic glomerulosclerosis	15	3	20	3	1	33

demonstrated normal or Grade 2 eyegrounds, hypertension, proteinuria, and fatty casts or fat-laden epithelial cells in their urinary sediment. In those instances thought to be diabetic glomerulosclerosis the patients demonstrated hypertension, diabetes, proteinuria, fatty casts or fat-laden epithelial cells in their urinary sediment, and microaneurysms in their eyegrounds, in short, most or all of the changes associated with the Kimmelstiel-Wilson syndrome. Although a more careful clinical evaluation of patients with chronic glomerulonephritis may lead to a better differentiation between nephrosclerosis and glomerulonephritis, such would not appear to be the case with diabetic glomerulosclerosis and nephrosclerosis.

In seven patients in whom a clinical diagnosis of renal disease was made, the biopsy revealed essentially normal kidney. Two of these clinically had acute pyelonephritis. Since this can be a focal disease, it is not inconceivable that the involved area was missed by the biopsy needle. Two others had an abnormal urinary sediment not characteristic of any disease, and in each instance renal biopsy failed to reveal renal disease. One patient with hematuria of several years' duration and without any other evidence of renal disease had a biopsy interpreted as normal. Of the remaining patients, one was thought to have nephrosclerosis, but renal biopsy was normal, and one was thought to have a "myeloma kidney."

Of the six patients misdiagnosed clinically as having pyelonephritis, two had chronic glomerulonephritis and two had normal biopsies, as has already been discussed. In the four in whom pyelonephritis was missed prior to biopsy, one clinically had an unknown disease manifest by azotemia; one was thought to have nephrosclerosis; one, glomerulonephritis, and one, nephrocalcinosis.

Acute renal insufficiency due to "lower nephron nephrosis" was correctly diagnosed in two patients who had typical histories, but it was missed in two. One of these was a deaf-mute imbecile who could give no history but was thought to have terminal chronic glomerulonephritis, and one was an alcoholic who, again, could give no adequate history. This latter patient has been reported in greater detail elsewhere.[13] In both of these patients the period of oliguria usually seen in this syndrome was not observed and probably occurred prior to hospitalization.

Each of the following diseases was missed: amyloidosis, polycystic disease, and metastatic carcinoma.

Lupus erythematosis was suspected in three instances. In each instance a thickened glomerular basement membrane was found in the biopsy specimen and a definite pathological diagnosis could not be made.

Periarteritis nodosa was suspected in four patients. On biopsy one of these had acute and chronic glomerulonephritis; one had a diffuse arteriolitis consistent with malignant hypertension; one had nephrosclerosis, and one demonstrated only a thickened glomerular basement membrane. In none was the biopsy helpful in making the diagnosis, but it tended in each instance to rule out periarteritis nodosa.

In three patients there was no specific clinical impression except that renal disease

might be present, on the basis of the presence of casts in the urinary sediment. Only one of these demonstrated renal pathology, namely, nephrosclerosis.

In nine instances the pathologist was unable to make a definite diagnosis. Two of these had "chronic nephritis" histologically but could not be further classified. Six patients were found pathologically to have only thickening of the glomerular basement membrane, without other evidence of renal disease. One patient was thought on biopsy to have chronic pyelonephritis but at autopsy was proved to have polycystic disease.

COMMENT

In 1951 Iversen and Brun [1] reported the first large series of patients in whom needle biopsy of the kidney had been performed. They were able to obtain satisfactory specimens in 42 of 80 biopsy attempts and experienced no untoward complications. Since this time a number of additional reports have appeared using various modifications of the original procedure, making a total of about 600 reported biopsies (Table 2). These have confirmed its feasability and relative safety. There have been two deaths reported following the procedure.† It would appear from the reported cases that renal needle biopsy has a mortality rate of about 0.3% and morbidity rate of about the same.

TABLE 2.—*Summary of Biopsy Results*

	Total	Morbidity	Mortality
Iversen and others*.....	200	?	?
Alwall [3]	13	..	1
Parrish and Howe.....	169	2	..
Pirani and others [18].....	200	?	?
Others†	37	..	1
Total.....	619	2	2

* References 1 and 3.
† References 6, 9, and 14-16.

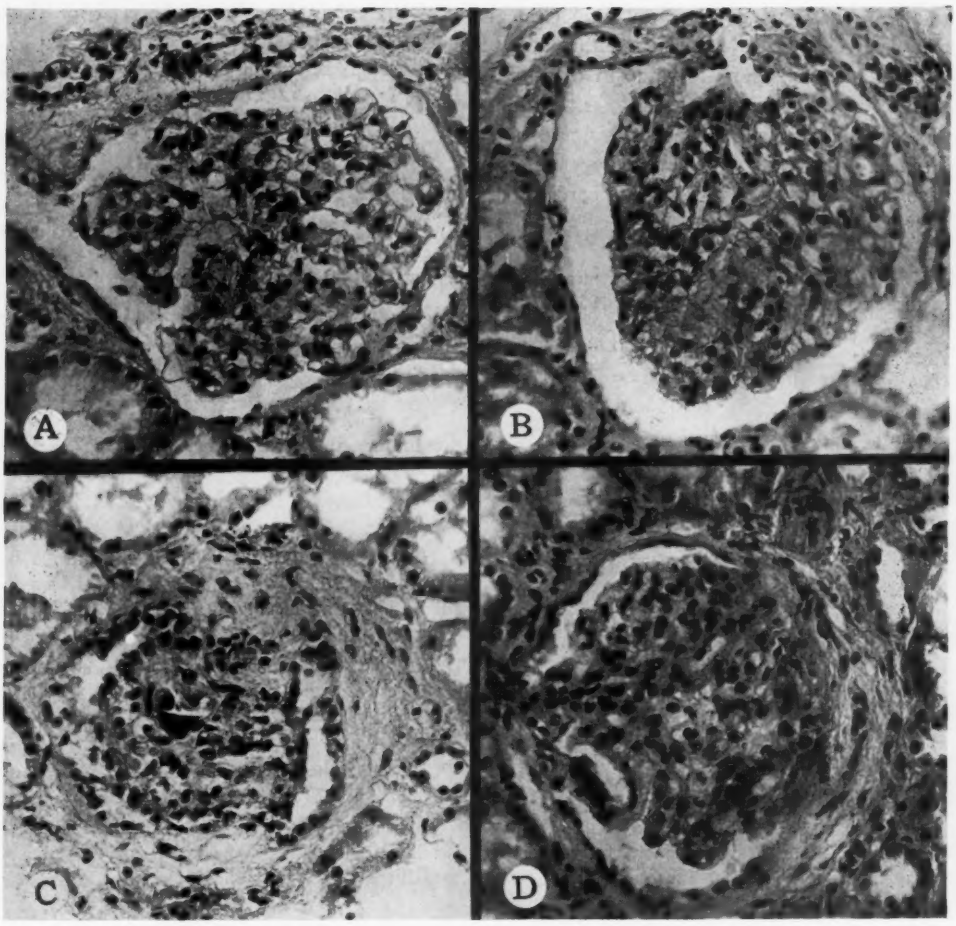
One of the most serious criticisms of needle biopsy is that it provides only a small amount of the entire organ and may miss important areas of pathology. The adequacy of the biopsy is, therefore, an extremely important factor in arriving at a diagnosis. It is our opinion that at least 10 glomeruli should be present, and preferably more, before a definite diagnosis can be made. To illustrate this, the Figure shows a biopsy specimen from a patient with signs, symptoms, and history suggestive of acute renal disease. This section shows glomeruli in several stages of disease, from almost normal to those showing epithelial crescents and evidence of subacute glomerulonephritis. A less adequate specimen might have been interpreted as focal glomerulitis (Fig., *A*), acute glomerulonephritis (Fig., *B*), or subacute glomerulonephritis (Fig., *C* and *D*).

Autopsies have been obtained in 13 patients subsequent to biopsy from one week to one year following the procedure. In only one of these were the biopsy and autopsy findings different. In retrospect, however, this was an error in interpretation rather than an inadequate biopsy.

From our results, needle biopsy provides a definitive diagnosis in about 91% of patients, confirming the clinical diagnosis in only 39% of cases. In at least 9% neither the pathologist nor the clinician can arrive at a definite diagnosis. In general, acute renal disease is fairly easily identified clinically. Acute glomerulonephritis was recognized 89% of the time; acute renal insufficiency with tubular necrosis was recognized 50% of the time, but 100% when history was adequate. Apparently clinical impression was better than biopsy in patients with acute pyelonephritis (which is in agreement with the findings of Kipnis and co-workers [6]). The etiology of chronic renal disease, however, was correctly recognized clinically in less than half the instances, even though renal disease was suspected. Needle biopsy in most instances provided the correct diagnosis.

Although our experience is limited, needle biopsy has not been helpful in cases in which there was no specific clinical impression, i. e., where renal disease was suspected but no definite diagnosis could be made on clinical grounds alone. Needle biopsy has also not

† References 2 and 14.



Renal biopsy specimen, showing the variations in different parts of the section.

been diagnostic in patients with lupus erythematosus (three patients), a finding contrary to previous reports,[15] or multiple myeloma (two cases), which agrees with other findings.[16]

The procedure has proved of value in such diseases as amyloidosis and in differentiating acute renal insufficiency with tubular necrosis, a reversible lesion, from other forms of renal insufficiency, where the prognosis is not as good and where artificial dialysis might not be of benefit. Its value in the diagnosis of diabetic glomerulosclerosis has already been pointed out.[17] Our results further confirm this and show that it allows distinction between arteriolar nephrosclerosis and diabetic glomerulosclerosis in diabetics.

SUMMARY

Renal biopsy established the diagnosis in 52% of the patients studied when the clinical impression was incorrect; it confirmed the clinical impression in 39% of instances, and in 9% neither the pathologist nor the clinician could arrive at a definite diagnosis.

It was of least help in acute glomerulonephritis, where the clinical impression was right 89% of the time. It was also of little value when no clinical impression could be made but when renal disease was thought to exist. Similarly, when acute pyelonephritis

was thought to be present on good clinical evidence renal biopsy was not confirmatory.

It was of considerable value in diagnosis in intercapillary glomerulosclerosis, chronic glomerulonephritis, nephrosclerosis, and rare diseases of the kidney such as polycystic disease, amyloidosis, and metastatic carcinoma.

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Regurgitant Esophageal Ulcer

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Regurgitant or peptic ulcers of the esophagus almost always occur as lesions that are associated with the short-esophagus type of esophageal hiatal hernia. A small percentage of these lesions [1] are congenital, but most occur as complications of the sliding type of esophageal hiatal hernia or of operations upon the gastric cardia.

CAUSATION

Any state which will allow acid gastric or alkaline duodenal secretions to come into prolonged contact with esophageal mucous membrane may produce this type of ulcer (Fig. 1).

Vomiting may rapidly produce ulcerative esophagitis. If the ulcerative process is not controlled, it eventually may lead to deep ulceration, formation of stricture, and shortening of the esophagus. Some patients who have regurgitant esophageal ulcers give a long history of functional vomiting. They usually have a hypersensitive gag reflex to the extent that they gag or vomit when they brush their teeth. They induce vomiting when they are under nervous tension. Roentgen studies of the esophagus and stomach for some years will disclose nothing abnormal, but finally a short esophagus will be found. Prolonged vomiting secondary to migraine, pregnancy, postoperative states, and obstructing lesions of the gastrointestinal tract also may produce esophageal ulcers. The vomiting of a patient who has an obstructing duodenal ulcer is particularly hazardous, since in such an instance the acid content of the secretions vomited is high and is capable of producing severe chemical esophagitis rapidly (Fig. 2). The necessity for control of the vomiting is urgent.

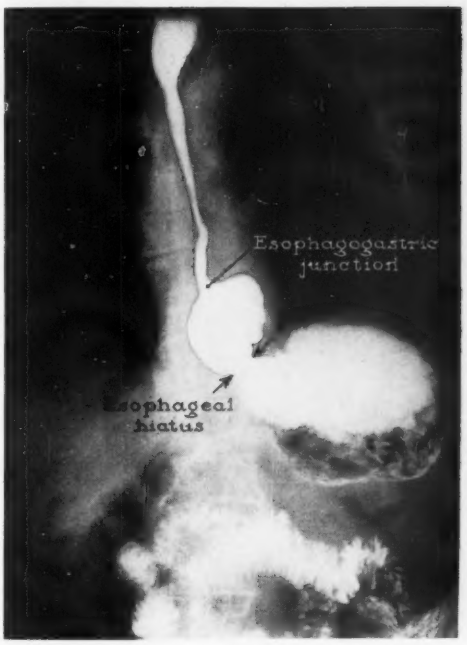

Fig. 1.—The patient was a 75-year-old man who had an obstructing carcinoma of the colon. This caused prolonged vomiting, ulcerative esophagitis, and finally a long stricture of the distal two thirds of the esophagus and a short-esophagus type of diaphragmatic hernia. (Retouched.)

The sliding type of esophageal hiatal hernia is the commonest cause of esophageal ulcers (Fig. 3). When this type of hernia is present, the esophagus has normal length. When the patient is standing, the force of gravity is exerted on the stomach in such a manner that it occupies a normal

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Fig. 2.—This patient had a duodenal ulcer with almost complete obstruction of the duodenum, which caused him to regurgitate into the distal part of the esophagus. The regurgitation produced ulcerative esophagitis, stricture at the esophagogastric junction, and a short esophagus. (Retouched.)

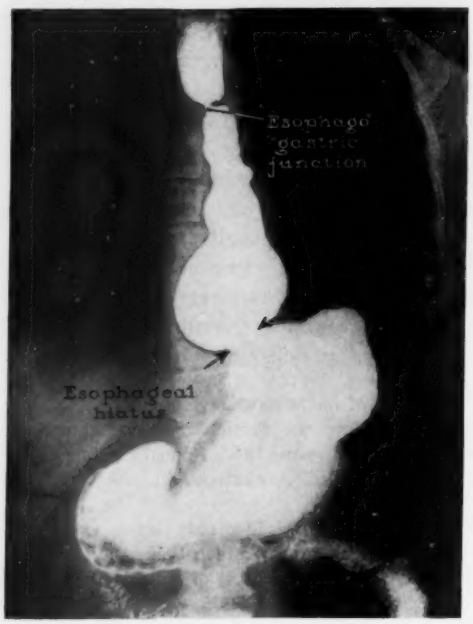
position. During recumbency or during periods when pressure is applied to the anterior abdominal wall, the cardia and variable amounts of stomach will be pushed into the thorax. During esophagoscopic examination done when this condition is present, it is found that the gastric cardia is incompetent, and yellow-tinged gastric juice will be seen to regurgitate freely into the lower part of the esophagus. Even so, ulceration of the esophagus develops in only a small percentage of patients who have the sliding type of esophageal hiatal hernia. It is surprising that such ulceration does not occur more often among patients with this type of esophageal hernia.

It has been reasoned that the most hazardous period, so far as the integrity of the esophagus is concerned, is during sleep. At that time the patient is recumbent and gastric juice regurgitates into the esophagus. Also, during sleep gastric juice is not neutralized by the intake of food for a long period.

Operations on the gastric cardia may produce ulceration of the esophagus. Unfortunately, the hazard of operating on benign lesions, such as cardiospasm and stricture of the distal portion of the esophagus, has not been generally recognized. Various types of plastic operations have been used to treat cardiospasm (Fig. 4). Operations which involve incision into all layers of the esophagus, including the mucous and submucous layers, are followed by the development of esophageal ulcers in a high percentage of cases. Some time may elapse before these ulcers become manifest (Fig. 5). Such surgical procedures should be condemned.

Esophagogastrectomy is an operation that has to be done for carcinoma involving the cardia or lower part of the esophagus. This operation at times is complicated by the formation of regurgitant esophageal ulcers, in spite of the fact that in the presence of

Fig. 3.—The patient was a 63-year-old woman who had a diaphragmatic hernia of many years' standing, with a history of regurgitation into the distal part of the esophagus. The regurgitation eventually caused marked shortening of the esophagus and a stricture at the esophagogastric junction. (Retouched.)



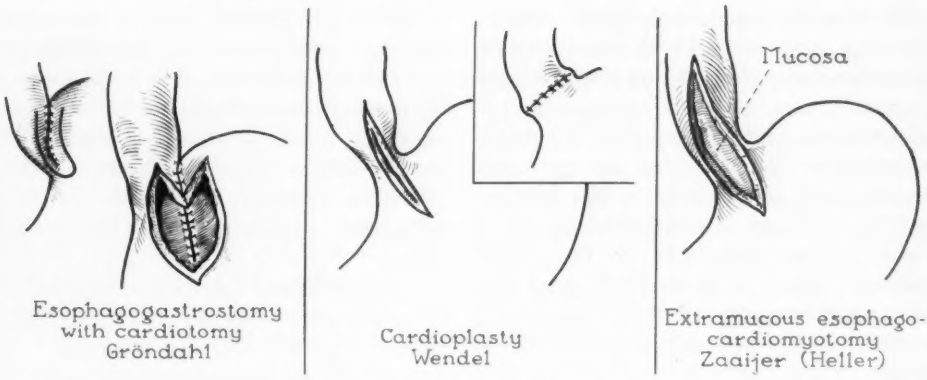


Fig. 4.—Operations that have been done on the cardia for cardiospasm. It is important that esophagogastrostomy or cardioplasty, as illustrated, not be done. If surgical intervention is necessary for this lesion, extramucous esophagocardiomyotomy is the safest operation that can be done. (Reproduced, with permission of the publisher, from Olsen, A. M.; Harrington, S. W.; Moersch, H. J., and Andersen, H. A.: The Treatment of Cardiospasm: Analysis of a 12-Year Experience, *The Journal of Thoracic Surgery,* St. Louis, The C. V. Mosby Company, 1951.)

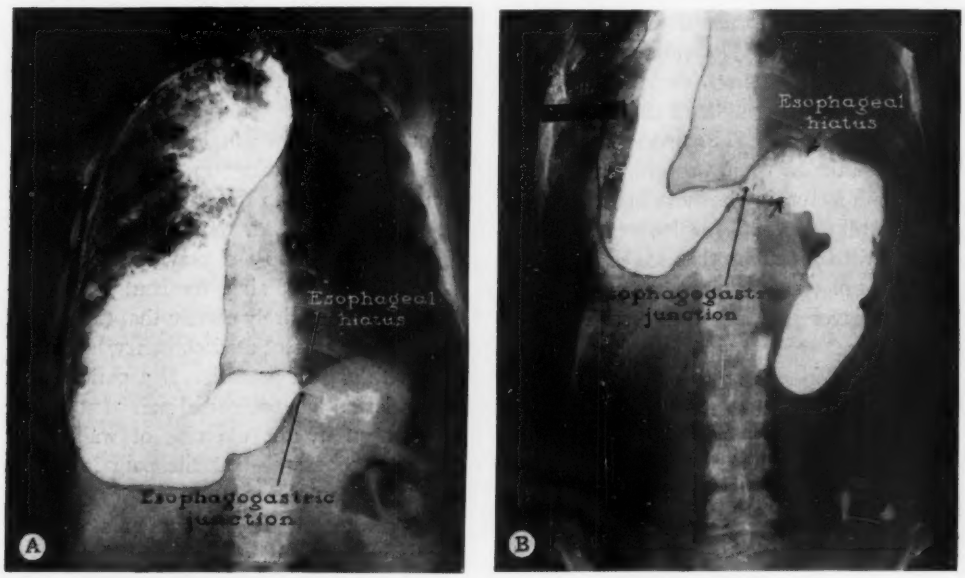


Fig. 5.—The patient was a 45-year-old woman who had marked cardiospasm which could not be successfully treated by dilatation. In October, 1948, she underwent esophagogastrostomy. Ulceration developed at the esophagogastric junction, and the patient eventually suffered a fatal hemorrhage. *A,* preoperative roentgenogram; *B,* postoperative roentgenogram. (Retouched.)

carcinoma of the stomach the acid value of gastric secretions usually is low. Esophagogastrectomy is an operation that should be avoided, in the case of benign lesions, if it is at all possible, since it completely abolishes the sphincter mechanism of the gastric cardia.

Neuman and Ellis [2] have studied the operation of esophagogastrectomy experimentally in dogs with special reference to methods of prevention of the complications of regurgitant esophagitis and esophageal ulcer. Pyloromyotomy, pyloroplasty, and gastrojejunostomy are gastric-drainage procedures which they employed to try to prevent regurgitation of acid gastric or alkaline duo-

denal secretion into the esophagus. Pyloromyotomy in association with removal of all the acid-secreting part of the stomach gave the best results. Gastrojejunostomy or pyloroplasty done in association with esophagogastrectomy, with removal of the acid-secreting part of the stomach, was followed by a high incidence of esophagitis and ulceration of the esophagus. None of the gastric-drainage procedures protected the esophagus when 20% to 30% of the acid-secreting portion of the stomach was allowed to remain.

Esophagocardiomyotomy (modified Heller operation) seems at present to be the safest operation to do for cardiospasm, if surgical treatment is necessary (Fig. 4). This operation cuts the musculature of the cardia as well as that of the adjacent portion of the esophagus and stomach down to the submucosal layer in a longitudinal direction (Fig. 4). No attempt is made to suture these layers. The length of the incision has been variable, depending upon the surgeon. Length of the incision, however, may be an important factor in the development of the complication of esophageal ulcer after this operation. It may be that excessively long incisions or the breaking-through of the mucosal layer are factors which are likely to produce regurgitant esophageal ulcers after this operation. Esophagocardiomyotomy has been followed by fewer such complications than any other plastic operation done on the cardia for cardiospasm.

The results of proper dilation of the esophagus by means of the Plummer hydrostatic bag have been so excellent, for most patients, that esophagocardiomyotomy should be reserved for such patients as do not respond to this type of dilation.

Additional preventive measures will be discussed in the section devoted to treatment.

SYMPTOMS

Dysphagia, retrosternal burning, epigastric pain, pyrosis, vomiting, and hemorrhage are the commonest symptoms of regurgitant ulceration of the esophagus.

Almost all patients with a regurgitant esophageal ulcer have a short-esophagus type of hiatal hernia. The shortening of the esophagus is the result of fibrosis in the muscular layers of the esophagus. The fibrosis, in turn, occurs as a complication of chronic or recurrent esophagitis. At times, esophageal stricture will occur for the same reason.

An incompetent sphincter exists, and the symptoms which it causes are classic. During recumbency, stooping, or straining, sour gastric juice regurgitates into the mouth. In obese patients these symptoms will abate as weight is reduced. Any situation which increases intra-abdominal pressure, such as the wearing of tight clothing around the abdomen, will aggravate these symptoms.

Frequently, a "burning" pain is experienced high in the epigastrium and in the retrosternal region. This pain is worse when the patient is in the recumbent position, when gastric juice regurgitates into the esophagus. In some patients the pain becomes so extreme that they sleep sitting up in a chair. The pain may extend to the back at the level of the 10th to the 12th thoracic vertebrae, or it may extend into the cervical region and down the arms. Fairly frequently it is impossible to be entirely certain that the patient does not have associated coronary heart disease with angina pectoris. If a patient with such a lesion has precordial pain that can be brought on by the exercise of walking, it is safest to assume that the pain is due to coronary heart disease.

Approximately 18% of patients with regurgitant ulcers of the esophagus have an associated duodenal ulcer.[1] In such an instance the symptoms of duodenal ulcer also are present.

Most patients who have diaphragmatic hernias are aerophagic. The symptoms of upper abdominal distention and "fullness" extending up over the left anterior part of the thorax are common. When the stomach is distended with air, exaggerated consciousness of the presence and functioning of the heart becomes common. Patients thus affected come to their physicians worrying

about heart disease. The foregoing symptoms can be abated by belching, which is common.

Dysphagia is the commonest symptom of regurgitant ulceration of the esophagus, and it may occur in two ways: 1. It may be the result of esophageal spasm which comes about secondary to the esophageal ulcer and the diaphragmatic hernia. 2. It may be the result of stricture, which is a relatively frequent complication. If the dysphagia is due to spasm, it is intermittent in character and may be as severe when cold liquids are taken in as it is when solid foods are ingested. If it is the result of esophageal stricture, it is constant and is most marked when solid foods are ingested.

Hemorrhage is rather common. The amounts of blood lost may be microscopic in amount or they may be exsanguinating.

In a series of 170 patients with regurgitant ulceration of the esophagus seen at the Mayo Clinic in a 10-year period,[1] 38 complained of hematemesis, 20 complained of melena, and 16 said they had had hemorrhages of such severity that blood had to be transfused. One patient had received blood by transfusion eight times; three had required blood five times; one had required it four times; another one, three times; two required blood twice, and eight required it once. During this period there were three fatal hemorrhages.

Sometimes the bleeding is slow, and it may be unnoticed until the symptoms of rather marked secondary anemia develop.

Loss of weight may develop if the complication of stricture occurs.

RECOGNITION OF THE LESION

Roentgenologic Findings.—The esophagus will be seen to be shortened and may appear slightly dilated. The esophagogastric junction will be located at variable levels above the diaphragm. It may be anywhere from just above the diaphragm to as high as the level of the aortic arch. The constriction, if pronounced, will extend 1.5 to 2 cm. in length. If the lesion is the result of persistent prolonged vomiting, a short esophagus may be seen, with a diffuse fusiform stricture involving the distal half or more of the esophagus. The gastric folds can be seen extending through the diaphragmatic hiatus into the thorax. The intrathoracic portion of the stomach may be narrowed in such a way that it appears to be part of the esophagus below a stricture. If the patient is examined in the Trendelenburg position, reflux from the stomach can be demonstrated.[3] When minimal changes are present, the roentgenologist may call the esophagus and stomach "normal." If symptoms or roentgenologic findings suggest regurgitant ulceration at the esophagogastric junction, esophagoscopy should always be done to identify the lesion and to rule out carcinoma.

Esophagoscopy.—When a normal person undergoes esophagoscopy, it is usually difficult to introduce the esophagoscope past the final 1.5 to 2 cm. of the esophagus if the procedure is done with the patient under the influence of local anesthesia. The tip of the instrument must be directed to the left and anteriorly. Generally, it is necessary to exert slight pressure and to wait for the musculature of the esophagus and diaphragm to relax. After this occurs, yellow-tinged secretion is seen to gush from the stomach and into the lower part of the esophagus. There is evidence of sphincteric reaction at the cardia. In people who have esophageal hiatal hernias of the short-esophagus or sliding type, this sphincteric action is lacking. It is possible to see yellow-tinged gastric secretion in the middle and lower third parts of the esophagus. It is easy to pass the distal end of the esophagoscope into the upper part of the stomach. The same observations may be made after some of the cardioplastic operations done for cardiospasm or in all patients who have undergone esophagogastrectomy.

Prolonged exposure of the esophagus to gastric juice usually will cause esophagitis. The mucous membrane becomes redder than normal. As the inflammatory reaction becomes severer, linear superficial ulceration will develop between the longitudinal mucosal folds at the esophagogastric junction. If the process is severe, a deep, in-

durated ulcer may be seen on the esophageal side of the esophagogastric junction. It may have a nodular base or be covered with a gray-white exudate. The ulcer will bleed readily when touched, and it is impossible to distinguish it from carcinoma without biopsy. The ulcer, when deep, does not heal readily.

A common complication is formation of stricture. Generally, this stricture is short, unless it has been produced by prolonged vomiting. It is seldom as dense as a lye stricture, and as a rule it is easy to dilate.

TREATMENT

Prevention.—The most important aspect of treatment is the prevention of such a lesion. Some of the preventive aspects relating to prior operative procedures have been discussed under Causation. At present, only a small percentage of diaphragmatic hernias of the sliding type are repaired. Most are small and cause very few symptoms. These symptoms, when present, generally can be eliminated by reduction of weight, if the patient is obese, and by avoiding pressure on the abdomen. If, however, the patient has the classic symptoms of an incompetent cardia and esophagitis, it is best to repair the hernia to restore competency of the cardia and to obviate the risk of the development of regurgitant esophagitis, ulcer, stricture, and short esophagus.

It is best not to treat benign lesions of the lower part of the esophagus surgically until all conservative measures have been tried and found ineffective. Cardiospasm and benign stricture of the esophagus can be treated successfully by proper esophageal dilation in the majority of instances. As a rule, the end-result is better and the risk of development of a regurgitant ulcer is far less than would be the case if any of the presently used operations for these lesions were employed. If an operation must be done, esophagocardiomyotomy (modified Heller) seems to be the safest procedure to use.

For patients who vomit from whatever cause, everything should be done to eliminate the cause of vomiting as rapidly as possible. The patient whose vomiting is on a functional basis should be warned to stop this habit immediately.

Definitive Treatment.—After a regurgitant ulcer has formed, no treatment known at present is altogether satisfactory. In general, most patients can be treated by their following a medical program.

Medical Program.—This consists in the use of an ulcer diet and antacids. Patients should be advised to sleep with the head of the bed elevated 6 to 8 in., so that the force of gravity is utilized to keep acid gastric secretions in the stomach. Two blocks of wood of the desired height can be placed under the legs of the head of the bed to accomplish this elevation.

Patients who have sufficiently troublesome dysphagia should have the benefit of esophageal dilation, performed by the passage of esophageal dilating sounds over a previously swallowed silk thread, used as a guide. Generally, the esophagus can be dilated up to the diameter of a 45 or 50 F. sound, depending on how dense the stricture is. If symptoms warrant, dilation will have to be repeated.

Obese patients should lose weight, should not wear tight undergarments, and should avoid stooping-over positions. These are factors which increase intra-abdominal pressure and force gastric secretions into the esophagus.

Surgical Treatment.—It is beyond the scope of this paper to go into any detail regarding surgical treatment. However, some of the operations which have been used can be mentioned. In instances in which there is only moderate shortening of the esophagus, Harrington [4] has been able to suture the diaphragm above the stomach after the diaphragm has been paralyzed by phrenic-nerve interruption. Wangensteen and Leven [5] have performed subtotal gastric resection in an attempt (1) to reduce acidity and digestive capacity of the stomach and (2) to speed up the emptying time of the stomach. In a review of the records of a group of Mayo Clinic patients over a 10-year period,[1] it was

found that nine patients who had rather severe symptoms underwent this operation. Seventy-five to eighty per cent of the stomach was removed. Five had excellent results; two obtained good results and two were regarded as having poor results.

Allison [6] has performed partial esophagectomy and esophagoenterostomy for patients who have not responded to a conservative program. The rationale for this operation is elimination of the possibility of regurgitation of gastric contents into the lower part of the esophagus. A surgical procedure of this magnitude should be used only if conservative measures have failed and symptoms are severe. At our present stage of knowledge, such an operation would be indicated for any patient who has experienced repeated hemorrhages or who has intractable pain from his esophageal ulcer. It should also be considered for those patients who have had dense strictures of the esophagus and for whom repeated esophageal dilations have been a failure.

SUMMARY

Attention is called to the important lesion known as regurgitant or peptic esophageal ulcer. Most of these lesions occur secondary to esophageal hiatal hernia of the sliding type or to operations on the cardia. The esophagus becomes short and usually strictured as a result of fibrosis in the muscular layers of the esophagus, caused in turn by chronic esophagitis.

The symptoms, roentgenologic findings, esophagoscopic picture, and treatment are discussed.

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Esophagitis, Hiatus Hernia, and Cardiospasm

Surgical Considerations

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Esophagitis is present in only a small minority of the more than 500 patients with hiatal hernias and cardiospasm who are seen at the Lahey Clinic annually. This report will be concerned with only those cases complicated by esophagitis. The majority of small and even large hiatal hernias reduce readily on change of position and frequently are characterized by litte or no symptomatology. They are simply noted in passing by the fluoroscopist and are not considered an indication for medical or surgical therapy.

Nevertheless, esophagitis, when it develops, is a serious complication, and, inasmuch as several factors may be involved, each patient must be treated on an individual basis and followed for a long period of time. At the Lahey Clinic we have studied almost 100 cases of esophagitis in its various manifestations. A number of these have been isolated cases of inflammation of varying degrees, usually in the lower esophagus; some patients have, in addition, the sliding type of diaphragmatic hiatal hernia; some, the condition which is called cardiospasm, and some patients have had resections of the cardia and lower esophagus for benign or malignant lesions.

Seventy-two of these cases have been studied in detail by Dr. Walter B. Hoover and have been reported previously. It was pointed out at that time that the clinical picture varies widely. Thus, many patients had only a mild dysphagia and upper gastrointestinal distress. Others, however, had severe incapacitating pain, malnutrition, slight or massive hemorrhage, and even perforation.

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PATHOLOGY AS SEEN AT SURGERY

Patients who come to surgery have shown a marked degree of mucosal change (Fig. 1). The mucosa is abnormally brilliant red and is succulent. Frequently there are tiny ulcers between the granulomatous areas in the mucosa, which bleed easily on manipulation. In some cases a definite ulcer crater has been demonstrated, usually in the epiphrenic region, but this has occurred rarely. Fibrosis, on the other hand, is common in the lower esophagus. It replaces the muscle, both longitudinal and transverse, and accounts for the

Fig. 1.—Chronic esophagitis with stricture. Resected specimen, showing lower esophagus and upper stomach. The mucosa is ulcerated, and the muscle layers have been replaced by fibrous tissue.

Fig. 2.—Chronic aspiration pneumonitis of many years' duration associated with chronic esophagitis and cardiospasm.

narrowing of the lumen. In long-standing cases the periesophageal tissues are involved in the inflammation and sharp dissection is required to separate the esophagus from the mediastinal pleura and the root of the lung. Frequently a marked gastritis is also present, and in 4 of the 72 cases reported by Hoover from this clinic duodenal ulcer was present and there was a history of perforation.

Cases complicated by cardiospasm and the development of a megaesophagus show a fibrous constricting ring at the cardia. In addition, there is often an advanced degree of dilatation, hypertrophy, and tortuosity of the entire esophagus. Chronic pneumonitis may be present in one or both lungs from aspiration of esophageal contents over a period of many years (Fig. 2). Three cases of megaesophagus had a carcinoma of the esophagus in addition.

SURGICAL CONSIDERATIONS AND REPORT OF CASES

It is to be emphasized again that for the simpler types, which represent the majority, medical measures alone or medical measures combined with periodical dilatation are sufficient to maintain the patient in comfort and good nutrition. Many patients can be taught to perform the dilatations themselves on a weekly or biweekly basis (Fig. 3).

For patients with esophagitis with cardiospasm, or even those with early fibrous stricture, medical measures with periodic dilatations likewise may suffice. If surgery seems wise, the simpler Heller operation should be utilized first. Although the improvement in the megaesophagus may be only slight, a good functional result may be expected.

Far-Advanced Chronic Undilatable Stricture

In the past, far-advanced chronic stricture which cannot be dilated has proved to be an exceedingly difficult surgical problem (Fig. 4). It has been our feeling that in many of these patients who are malnourished, anemic, and show general debility a preliminary gastrostomy or jejunostomy should be carried out and a period of three months or more

Fig. 3.—Chronic dilatable esophagitis and stricture in an 18-year-old girl; managed by conservative measures plus weekly dilatation by the patient herself.

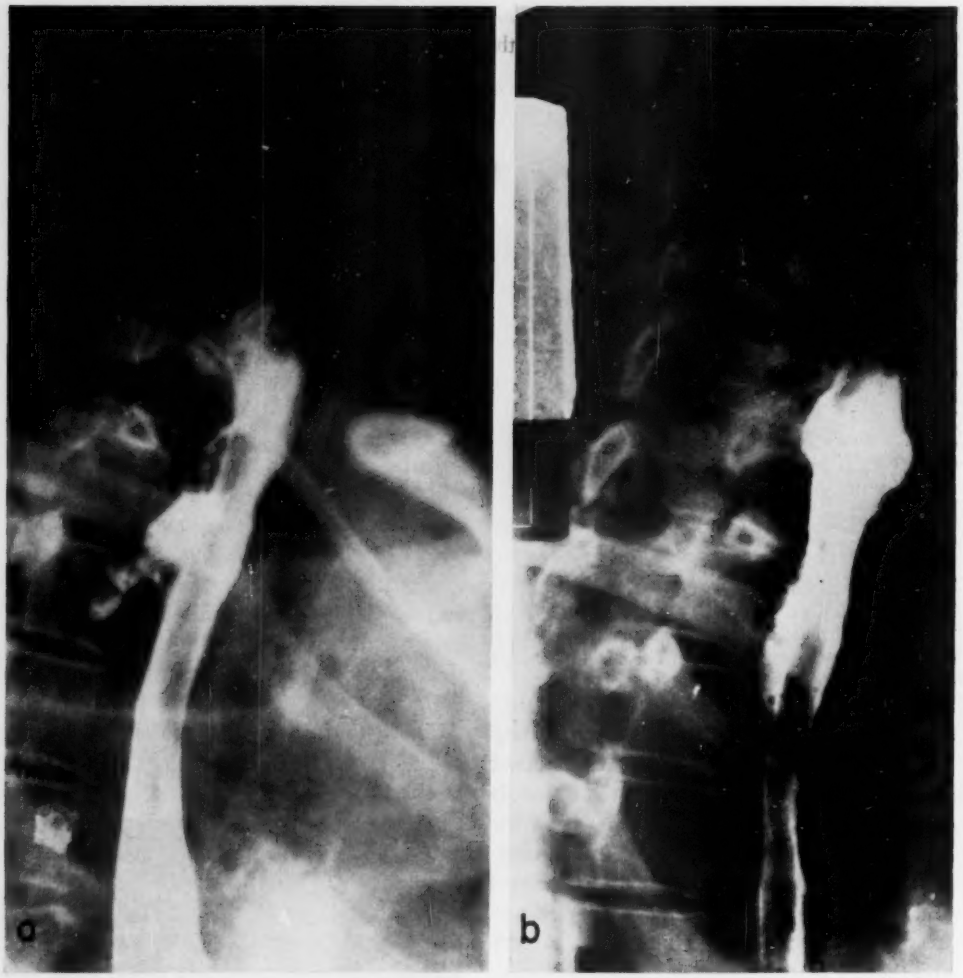

Fig. 4.—High esophagitis with stricture in a 21-year-old girl. History of dilatations for many years; recently undilatable. Plastic operation performed on esophagus at level of superior strait. (*a*) Anticipated postoperative leak at suture line; (*b*) healing and good lumen are shown. Patient was taught to dilate the esophagus herself weekly. (From Boyd, D. P., *The Surgical Clinics of North America,* Philadelphia, W. B. Saunders Company, 1955.)

allowed to elapse before radical surgery is contemplated (Fig. 5). The presence of a gastrostomy does complicate the definitive surgical procedure, but the improvement in the patient's condition makes up for any possible disadvantage.

In the beginning we employed conservative resections of the lower esophagus and cardia for this condition but found that esophagitis recurred in the postoperative period (Fig 6). This was equally true of the patients who had a megaesophagus. In addition to recurrence of symptoms and secondary stricture, there are two other hazards to this procedure that must be taken into account. One is the development of the so-called vagotomy effect at the pylorus; the second is hemorrhage from the residual esophagus.

CASE 1.—A woman of 55 years had undergone periodic dilatations for benign stricture of the esophagus at the clinic for a period of 10 years. When it became apparent that a dangerous amount of force was required to achieve dilatation and a severe systemic reaction occurred after an attempt at dilatation, surgical intervention was considered

and carried out. Local resection of the lower esophagus and the gastric cardia was perfo. ned. Before the patient left the hospital, although she was swallowing well, she informed us that she had distress in the epigastrium, particularly in the substernal area. In less than three months after operation, dilatations were again necessary and are still being carried out at regular intervals three years after resection.

CASE 2.—A woman of 32 years had had dilatations for many years for stricture of the lower esophagus with megaesophagus (Fig. 7). A conservative resection of the tortuous lower third of the esophagus and the gastric cardia was carried out. Convalescence was uneventful. However, the

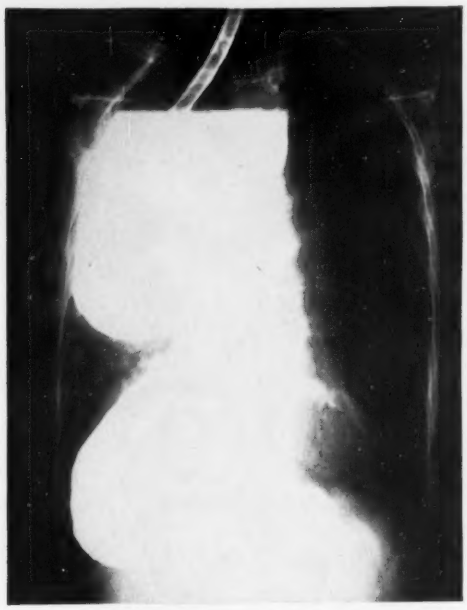

Fig. 5.—Far-advanced undilatable stricture with megaesophagus. Patient weighed 75 lb. Preliminary gastrostomy indicated.

patient was readmitted four months after operation because of a history of massive gastrointestinal hemorrhage. Esophagoscopy demonstrated severe esophagitis in the lower half of the remaining esophagus, with many areas of ulceration. She was treated conservatively with transfusions, placed on a very strict medical regimen, and discharged from the hospital. One month later she was readmitted, again exsanguinated. This time the middle third of the esophagus was resected and esophagogastric anastomosis was performed above the aortic arch. The patient has remained well to date without further evidence of esophagitis (Fig. 8).

CASE 3.—A man of 55 years had moderately severe cardiospasm complicated by a large diverticulum just above the cardia. Because of the presence of this diverticulum it was thought that surgery was indicated rather than dilatations, and a conservative resection was carried out. Early in his convalescence the patient began to regurgitate almost everything that was taken by mouth. Fluoroscopy after a swallow of barium revealed that the pylorus was completely occluded, and in the second postoperative week gastroenterostomy was carried out. Convalescence was uneventful.

Comment.—It is apparent from this discussion and these case reports that the problem of the surgical treatment of the undilatable stricture is fraught with surgical complications. It is our policy at the present time to attempt to prevent the complications which have been shown to occur by two specific steps. First, a sufficiently radical resection of the esophagus should be performed. It is not clear why the upper esophagus should be more immune to recurrent ulcerations than the lower part, but in a small experience this has proved to be so. In addition, it is very important to perform a pyloroplasty or gastroenterostomy to permit proper emptying of the stomach and to prevent regurgitation. If these two precautions are observed, the treatment of the chronic severe stricture of the lower esophagus will be manageable surgically.

ESOPHAGITIS WITH MARKED HYPERACIDITY

The experience of Wangensteen and others, including ourselves, has indicated that there may be certain cases of esophagitis in which the primary disturbance is in the so-called ulcer diathesis. If the esophagitis has not progressed to the point of severe stricture, it is reasonable that subtotal gastrectomy and vagotomy be applied to these cases. I do not believe that gastrectomy should be used in advanced cases, because this operation will seriously complicate resection of the lower esophagus should this be necessary later. However, the careful individualized study which these cases demand will occasionally indicate the feasibility of gastrectomy.

ESOPHAGITIS WITH DIAPHRAGMATIC HERNIA

The complication of mild esophagitis does not necessarily indicate the need for repair

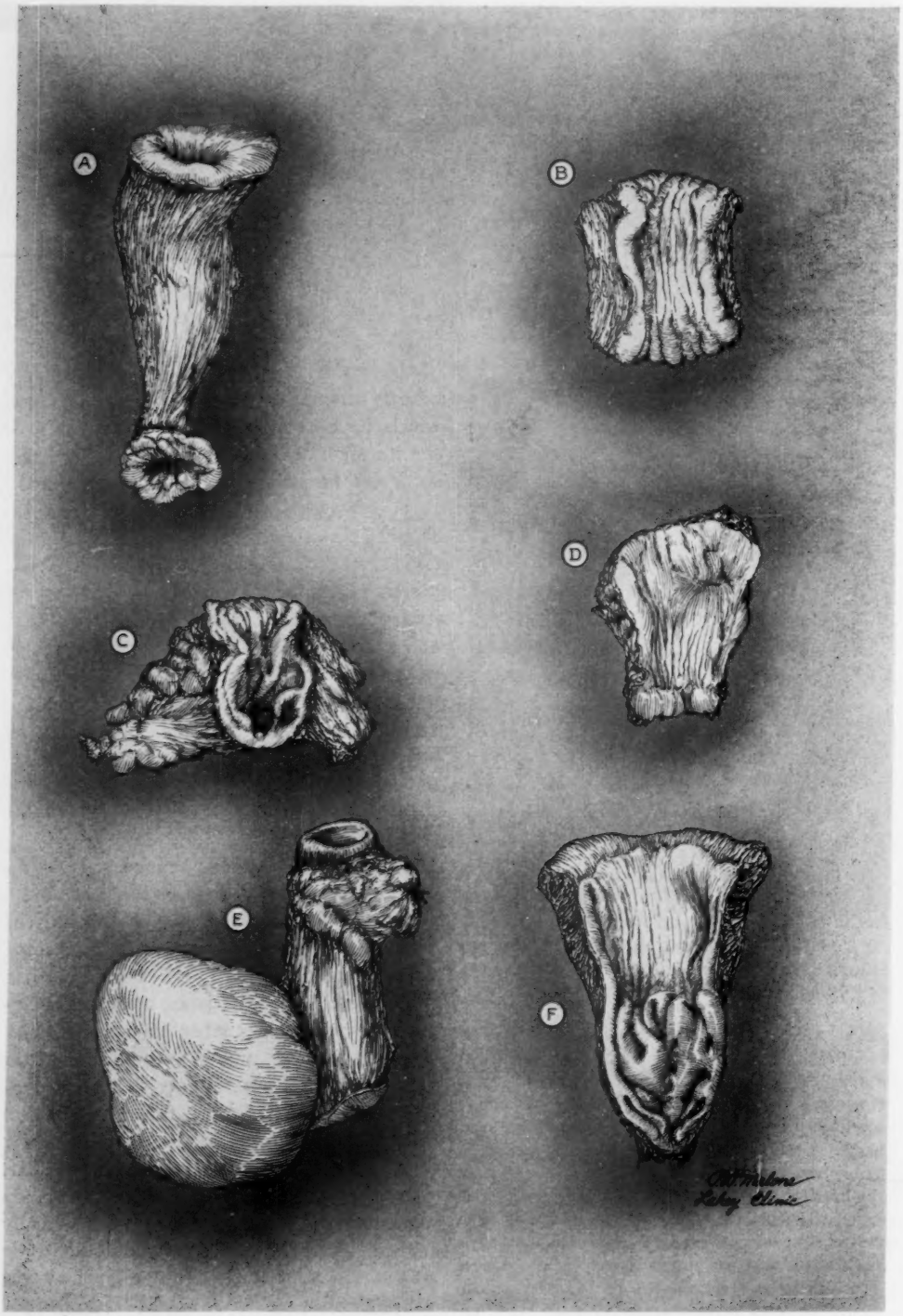

Fig. 6.—Specimens removed by conservative resection of the cardia and lower esophagus. All cases except *A* and *E* were poor results. (From Hoover, W. B., *Annals of Otology, Rhinology and Laryngology,* St. Louis, Annals Publishing Co., 1950.)

Fig. 7.—Long-standing esophagitis, stricture, and cardiospasm. Conservative resection of cardia and lower esophagus. Symptoms recurred immediately, and later, severe hemorrhage. Relieved by radical esophagectomy and pyloroplasty.

of a sliding hernia at the hiatus. As criteria for repair we have utilized the following: marked clinical symptoms, gastrointestinal bleeding, and a hernia which is not reduced with changes in position at the fluoroscopy table.

Regardless of the severity of the esophagitis and even if benign stricture is present, a simple transthoracic repair of the hernia should be carried out first. This will frequently be sufficient to permit the esophagitis to heal. Medical management and even dilatations may later be necessary.

Emergency Operations in Esophagitis

Occasionally, hemorrhage from esophagitis or esophageal ulceration may be sufficiently severe to demand immediate surgical intervention, as indicated by the following case report.

Case 4.—A nurse, 48 years of age, was admitted by ambulance. She had been in her local hospital for 10 days and had received 42 pt. of blood for bleeding of the upper gastrointestinal tract. At the time of her admission to the New England Baptist Hospital she was vomiting blood.

On admission, her color was pale, her blood pressure was not obtainable, and the hemoglobin was 5 gm. Several units of blood were given rapidly, and, although the patient's condition improved slightly to the point that the blood pressure and pulse were obtainable, she continued to vomit blood repeatedly. In the early evening she was taken to the operating room, and an abdominothoracic incision was made. The stomach was opened and was found to contain bright red blood, but no point of hemorrhage could be ascertained. The incision in the anterior wall of the fundus of the stomach was carried up the esophagus, laying the esophagus open. The lower esophagus, while showing the typical redness and granulation of esophagitis, presented no specific bleeding point. It was still apparent that the bleeding was coming from higher up the esophagus. At the level of the inferior pulmonary vein an area of ulceration with a crater was found in the lower esophagus. A moderate-sized artery was seen to be open and spurting in the center of this ulcer. The lower and middle esophagus was resected, and the gastric cardia was closed and anastomosed to the upper

Fig. 8.—Postoperative spastic occlusion of the pylorus relieved by gastroenterostomy. Specimen removed shown in Figure 6 *E*.

esophagus. The patient had an uneventful convalescence.

The other serious and urgent complication of esophagitis and esophageal ulcer is perforation. This casualty most frequently follows instrumentation and will not be considered here. Occasionally, however, an esophageal ulcer will perforate spontaneously.

CASE 5.—A patient came to the clinic for investigation of dysphagia and gastrointestinal disturbances. A barium series was begun at the clinic and showed esophagitis and a crater close to the diaphragm. The patient was sent home with instructions to return for a 24-hour x-ray plate. He was readmitted at two o'clock the following morning because of acute abdominal and thoracic pain. The physician who first saw him in the hospital was sufficiently astute to realize that something was wrong not only with his abdomen but also with his chest. A thoracic consultant was called. Thoracotomy was carried out within six hours of the onset of symptoms, and a perforation in the lower third of the esophagus was closed. Although empyema developed, and later there was transient hemiplegia from a cerebral accident, the patient left the hospital in good condition.

SUMMARY

The majority of cases of esophagitis may be managed by the gastroenterologist and the endoscopist. Careful supervision is essential, but many patients can be taught to carry out the dilatations themselves safely.

Patients with diaphragmatic hernia and marked esophagitis with regurgitation are greatly improved by repair of the hernia.

Patients with megaesophagus should be treated by the Heller operation, which gives symptomatic relief.

Severe esophagitis with or without the above factors may result in an undilatable stricture. At present it appears that radical esophagogastrectomy and pyloroplasty offer the greatest chance of cure.

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Hoover, W. B.: Esophagitis: A Clinical Evaluation, Ann. Otol. Rhin. & Laryng. **61**:1148-1157 (Dec.) 1952.

Treatment of Hypochromic Anemia with an Intramuscular Iron-Dextran Complex

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Anemia resulting from iron deficiency is one of the commonest diseases which we are called upon to treat, and although at first glance it would seem a simple matter to correct such an abnormality this is by no means always the case. Some patients are unwilling to take adequate amounts of iron by mouth; others show intolerance such as gastrointestinal disturbance to even small doses of the metal, and still others appear to be refractory, although the dosage is theoretically sufficient.

Apart from rare cases in which anemia results from inability to utilize iron, it can be corrected by (*a*) supplying iron in an acceptable form and (*b*) ensuring satisfactory conditions of pH in the stomach and upper small intestine. This, of course, assumes that the underlying cause, e. g., hemorrhage, infection, etc., has been dealt with. Nevertheless, cases occur in which either the first two conditions are not attainable or in which the degree of anemia is such as to require restoration of the hemoglobin in the shortest possible time.

Various methods of supplying iron parenterally have been tried in the past, but usually the development of undesirable local and general reactions has precluded their use in practice. The introduction of saccharated iron oxide, suitably prepared for intravenous injection, was therefore an important step forward in therapy. However, even this substance is not free from danger when it leaks into the subcutaneous tissues, and it can, on occasion, cause toxic reactions in certain persons.

It was, therefore, with much interest that we accepted the invitation to carry out clinical trials on a new iron complex which previous animal investigation had shown to be suitable for intramuscular administration, especially as we had had considerable experience with the original intravenous preparation, Ferrivenin, in its early days. It seemed to us that for a compound of iron to be of practical value when given intramuscularly it should fulfill the following requirements:

1. The technique of administration must be simple.

2. It should be free from undesirable local and general reactions.

3. It should be capable, by virtue of rapid and complete absorption, of producing a response as good as that of an intravenous preparation.

We have now given this intramuscular iron preparation to 30 patients suffering from hypochromic anemia, and full hematological investigation has shown that it does satisfy the above criteria. Five typical cases are described, and the hematological results are shown in detail in the accompanying Table.

CASE 1.—A. S., a married woman aged 56, stated that she had had anemia for many years but had never responded completely to treatment. A gastroenterostomy was performed in 1944 for peptic ulcer. For the last two years she had been dieting herself strictly, taking little more than tea and toast. She was admitted to hospital with acute bronchitis and was found to be severely anemic.

Initial hemoglobin, 31% (Haldane)

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St. Catherine's Hospital; Consultant Physician (Dr. Grunberg) and Medical Registrar (Dr. Blair).

Bone marrow, normoblastic

Occult blood not detected in feces.

Intramuscular iron totaling 3200 mg. was administered over a period of four weeks.

Hemoglobin at end of 4 weeks, 73% (Haldane)

Hemoglobin at end of 11 weeks, 99% (Haldane) without further iron therapy.

CASE 2.—K. C., a single girl aged 17 years, was admitted to hospital in December, 1953, with a provisional diagnosis of hematemesis which, however, was not definitely confirmed, although the barium meal showed a small gastric ulcer.

Hemoglobin, 60% (Haldane)

Treated "medically" and iron given orally.

Feb. 28, 1954, hemoglobin, 51% (Haldane). She admitted she was not taking her iron medicine, and she had not adhered to dietary instructions.

Bone marrow, normoblastic.

Intramuscular iron totaling 1950 mg. was given over a period of three weeks.

Hemoglobin at end of three weeks, 75% (Haldane)

Hemoglobin at end of six weeks, 105% (Haldane) without further iron therapy.

CASE 3.—B. C., a married woman aged 56, had complained of indigestion for two years, associated with nausea and occasional vomiting, especially after fatty foods; she also felt tired and occasionally "light-headed." She stated that she had been treated for anemia for about 10 years.

Hemoglobin, 41% (Haldane)

Bone marrow, normoblastic

Barium meal showed an irreducible hiatus hernia with a redundant esophagus

No occult blood was detected in the stools.

Intramuscular iron totaling 2200 mg. was given over a period of four weeks.

Hemoglobin at end of four weeks, 83% (Haldane).

CASE 4.—F. W., a married woman aged 44, complained of dyspnea on exertion, lassitude, and loss of appetite in March, 1954. Posterior gastroenterostomy had been performed 10 years previously for duodenal ulcer. Partial gastrectomy was performed in 1952 because of recurrence of ulcer.

Hemoglobin, 43% (Haldane)

Bone marrow, normoblastic

No occult blood detected in stools

Barium meal showed that the stomach filled normally and emptied via the stoma, which functioned well.

Intramuscular iron totaling 1950 mg. was given over a period of three weeks.

Hemoglobin at end of three weeks, 78% (Haldane)

Hemoglobin at end of five weeks, 95% (Haldane).

CASE 5.—J. U., a married man aged 42, was admitted to hospital with a history of having been treated for a number of years with repeated blood transfusions as a case of aplastic anemia. In actual fact, there is some doubt as to whether he took any of the hematinics prescribed for him. Barium meal, chest x-ray, and x-ray of the long bones were all normal. The fractional test meal showed a histamine-fast achlorhydria. There was no evidence of chronic blood loss.

Initial hemoglobin, 51% (Haldane)

Bone marrow, normoblastic.

Intramuscular iron totaling 2000 mg. was given over a period of 10 days.

Hemoglobin after 10 days, 77% (Haldane)

Hemoglobin after 1 month, 90% (Haldane), without further iron therapy.

Data in Five Cases of Hypochromic Anemia

	Week							
Case 1	0	1	2	3	4	9†	11†	15†
Hgb., % *	31	44	51	63	78	81	90	99
RBC, million	2.38	3.09	4.32	4.48	4.96	5.00	4.96	5.08
Reticulocytes, %	1	1	4	2	1	..	..	..

	Week				
Case 2	0	1	2	3	6†
Hgb., % *	51	64	70	75	105
RBC, million	2.53	4.17	4.35	4.60	4.90
Reticulocytes, %	1	2	2	1	...

	Week					
Case 3	0	1	2	3	4	8†
Hgb., % *	41	52	65	76	83	104
RBC, million	3.70	3.84	3.80	4.20	4.80	5.10
Reticulocytes, %	2	4	3	1	..	...

	Week					
Case 4	0	1	2	3	5†	12†
Hgb., % *	43	52	64	78	95	105
RBC, million	3.12	3.50	4.22	4.24	4.80	5.00
Reticulocytes, %	1	3	2	..	..	...

	Week			
Case 5	0	1	2	4†
Hgb., % *	51	77	85	90
RBC, million	3.11	4.68	4.90	4.96
Reticulocytes, %	4	8	1.5	..

* 100% hgb. (Haldane) = 14.8 gm. per 100 ml.
† After the end of the course of injections.

COMMENT

(1) *Method of Estimating Dosage.*—In theory, 100 mg. of iron is capable of raising the hemoglobin by 4%. For practical purposes, the simplest method of estimating the amount of iron required in a given patient is as follows:

Hgb.% deficit × 25 = mg. iron required to restore the hemoglobin to 100%

This amount may be increased by 50% to allow for replenishment of the depot iron. In some severe cases we have increased it by 80% without ill effect.

(2) *Frequency of Injection.*—The total amount of iron administered was given in divided doses commencing with two injections of 100 mg. each and continuing with 250 mg., on subsequent occasions. (The iron-dextran complex used contained 50 mg. iron per milliliter.) We adopted the routine of injecting on alternate days, but in two cases daily injections were given to avoid upsetting certain domestic arrangements previously made by the patients concerned. In both instances, no harmful effects were noted.

(3) *Technique of Administration.*—The site chosen in each case was the upper third of the outer side of the thigh, using the left and right limbs alternatively. The technique of administration was the same as for any other intramuscular injection, and no special precautions were taken apart from the usual attention to asepsis.

(4) *Local Reactions.*—In a few of the early cases some brownish discoloration was noted around the injection site, evidently due to the material leaking back along the track of the needle. This was avoided subsequently by the following device. After the point of the needle had been passed through the full thickness of the skin, and before the muscle was penetrated, the skin was drawn to one side so that the resulting track was Z-shaped. The discoloration was transient, however, and caused no disturbance to the patient.

As has been mentioned above, one of the disadvantages of intravenous iron therapy is the discomfort or actual tissue damage caused by accidental extravasation from the selected vein. The iron dextran complex under trial possesses a pH and tonicity which approximate closely to those of the tissue fluids. It would, therefore, be expected that no local reaction would be experienced other than the slight feeling of tension which accompanies any sizable intramuscular injection, and this expectation has been fulfilled.

(5) *General Reactions.*—Three of our cases were investigated and treated as outpatients, but the remainder were admitted to hospital and kept under observation for the duration of their course of injections. None showed any constitutional disturbance, and all claimed that they felt definitely better within 7 to 10 days after commencing treatment.

(6) *Absorption and Utilization.*—Experimental studies have shown that the iron dextran complex has a high degree of stability. In spite of this fact, it is not fixed locally by the muscle protein at the site of injection and is, therefore, readily absorbed. It will be seen from the accompanying Table that a significant increase in the hemoglobin level had occurred by the time the final injection was given, and this bears out the result of animal experiment. The ability of this complex to raise the hemoglobin content of the blood compares very favorably with that of iron injected intravenously.

SUMMARY

Clinical trials with an iron-dextran complex, suitable for intramuscular use, have been described.

The preparation has been given to 30 patients; no difficulty has been encountered either in administration or as a result of side-effects.

The response was satisfactory and was indistinguishable from that obtained with intravenous therapy.

Dr. Frank Fletcher invited us to take part in these trials, and he and Bengers, Ltd., provided us with adequate supplies of the new preparation. The Group Pathologist, Dr. R. M. Rawcliffe, and her technical staff carried out the bone marrow and other hematological studies.

A Bibliography of Internal Medicine

CHOLERA

ARTHUR L. BLOOMFIELD, M.D., San Francisco

The rationale of this bibliography is fully set forth in the introduction to a previous section (A Bibliography of Internal Medicine: Scarlet Fever, *Stanford M. Bull.* **10:** 114, 1952). Suffice it to say that it is designed mainly for readers with general interests, although within its scope it attempts to be definitive.

I have found no really comprehensive modern bibliography of cholera. Much of the early literature deals with descriptions of outbreaks or epidemics, and this phase of the subject is comprehensively dealt with by Hirsch (Ref. 10) as well as by C. Macnamara, in "A History of Asiatic Cholera," London, Macmillan & Co., 1876. A good general account of the disease is that of H. Harold Scott, in his "History of Tropical Medicine," Baltimore, The Williams & Wilkins Company, 1939, Vol. 2, p. 694. C. Liebermeister's "Cholera Asiatica und Cholera Nostras," Wien, Alfred Hölder, 1896, has appended to it a fairly comprehensive bibliography of the older literature. Finally, J. S. Chambers, in his book, "The Conquest of Cholera," New York, The Macmillan Company, 1938, gives in interesting detail the story of cholera, especially in the United States.

CHOLERA

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Carriers
Reference 21

Clinical
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Epidemiology
References 2, 7, 8, 9, 10, 14

General
References 1, 2, 4, 5

Immunity
References 12, 13, 15

Pathology
References 5, 6, 20

Serum therapy
Reference 18

Treatment, antibiotic
Reference 23

Treatment, with salts and fluids
References 3, 19

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From the Lane Medical Library.

Supported by a grant from the California Foundation for Medical Research.

1. Brigham, A. Treatise on Epidemic Cholera, Including an Historical Account of Its Origin and Progress to the Present Period, Hartford, Conn., H. & F. J. Huntington, 1832.

Although epidemics of what was pretty clearly cholera had been described at various times (Ref. 10), the modern history of the disease dates from the outbreak at Jessore, in India, in 1817. Brigham's book opens with a year-by-year description of the progress of this epidemic, which spread over India during the ensuing years but did not reach Asia Minor and China until 1823. In 1829 the disease crossed the Urals and in 1830 spread along the Volga, reaching Moscow. In 1831 it appeared in many parts of Europe, including Berlin. In this year it also reached England. (For detailed accounts of the various epidemics see Ref. 10.) Next come accounts of the disease from various parts of the world. In the cases seen by the writer in New York he describes the symptoms as follows: "First, diarrhoea, though often of only short duration, then nausea and vomit-

ing, though in some instances the vomiting was slight, to which succeeded a sinking of the circulation, coldness and blueness of surface, burning thirst, spasms and death. In most of the cases that I have seen, the discharges from the stomach and bowels were light colored, resembling arrow root and water or starch and water, and were without odor" (p. 104). In another account (p. 102) the stools are described as being "like rice water." "Besides the intestinal canal and skin all other organs furnished no secretion. Tears, pituita, saliva, and urine, the secretion of which is totally suspended; as to tears, the greatest anguish of dying, in full possession of the intellect, surounded by all that is at once endearing and afflicting, could not produce them." The thickness of the blood is remarked, and it is stated that leeches could procure none. "The accounts of this disease, from Asia, Persia, Russia, Poland, England, Canada and the United States, all agree." (p. 105). The descriptions of "Appearances on Dissection" follow; aside from the evidence of desiccation there is disagreement as to the significance of the findings. In some cases the gastrointestinal tract is said to show little; in others there are extensive lesions of the superficial layers.

As to treatment it is hard to see how physicians could have failed to note the obvious evidences of dehydration; instead, bleeding and leeching and the usual variety of meaningless drugs were advised. In one account (p. 168) it is stated "let two tablespoons full of common kitchen salt, dissolved in six ounces of warm water, be given immediately." That the writer had no rational basis for this prescription becomes clear when he adds: "energetic complete vomiting will probably be produced by the salt." However, he adds later (p. 176): "The patients treated in this manner, that is, with a solution of common salt, were often very soon restored to health, and could hardly be recognized after a few hours." On p. 243, however, a most interesting statement appears: "A few have been cured in New York by the injection of saline solutions into the veins. Dr. Rhinelander stated to the Board of Health of New York the case of Margaret Mehan, who was cured at Crosby Street hospital, by injecting into the veins twenty four ounces of a solution composed of one dram of carb. soda, and two drams of muriate of soda [common salt] dissolved in six pints of water. The operation was performed at 7 P.M. on July 21st [1832?]. Several other cases of cholera have been cured in a similar manner, both in this country and also in England, where the practice I believe originated. This practice is undoubtedly founded upon the fact, said to have been discovered by analysis; that the blood drawn from a patient affected with cholera, has lost a portion of its watery and albuminous parts, and also most of its natural saline ingredients."

There are introduced at this point two lectures by J. F. V. Broussais, of which the most interesting part is the discussion of contagion. The fact that several members of a household often had the disease "gives rise to the suspicion that there is a species of infection by which the patient communicates the disease to those who have charge of him." But by their number and vociferousness the anticontagionists vastly predominated at this time.

2. **Bell, G. H.** Treatise on Cholera Asphyxia or Epidemic Cholera, Ed. 2, Edinburgh, William Blackwood, 1832.

Cholera went under a variety of descriptions: cholera asphyxia, blue cholera, epidemic cholera, asiatic cholera, cholera morbus, etc.; many used the term cholera morbus for sporadic cases in distinction to the epidemic. This book, like many others at the time, deals with the whole subject. Worthy of mention, however, is the discussion on contagion. "Much stress has been laid on the fact that the Cholera has travelled along the banks of rivers. Undoubtedly it has done so; but in so far as regards India, the writers who rely so confidently on this fact, have not adverted to the peculiarity, that the progress of the disease along the banks of rivers, has not been

confined, as they seem to suppose, to navigable rivers. It has extended itself along the banks of rivers whether navigable or not" (p. 84). No one sensed the fact that the disease might be conveyed by contamination of the river water.

3. Documents Communicated by the Central Board of Health, London, Relative to the Treatment of Cholera by the Copious Injection of Aqueous and Saline Fluids into the Veins, *Lancet* **2**: 274, 1832.

The first approach to a rational therapy for cholera was by W. B. O'Shaughnessy (Proposal of a New Method of Treating The Blue Cholera Epidemic by the Injection of Highly-Oxygenated Salts into the Venous System, *Lancet* **1**:366, 1831-1832), who was impressed by the thick black blood and recognized the need of restoring it to an oxygenated or arterial state. This he proposed to do by injection into the vein of "oxygenated salts" such as potassium nitrate and potassium chlorate. Nothing came of this, but a little later (Experiments on the Blood in Cholera, *Lancet* **1**:490, 1831-1832) O'Shaughnessy reported analyses of blood from cholera patients which gave him a lead in the right direction. He found the blood "has lost a large proportion of its water, it has lost also a great proportion of its *neutral* saline ingredients" and that "of the free alkali contained in healthy serum, not a particle is present." He also found that "urea exists in the cases where suppression of urine has been a marked symptom" and that "all the salts deficient in the blood, especially the carbonate of soda are present in large quantities in the peculiar white dejected matters." O'Shaughnessy issued a larger report on these findings with therapeutic suggestions which was reviewed in critical if not hostile fashion later in the year (Report on the Chemical Pathology of the Malignant Cholera [Review] *Lancet* **1**: 929, 1831-1832). "when absorption is entirely suspended as in those desperate cases which are unhappily now of daily occurrence in this metropolis, the author recommends the injection into the veins of tepid water holding a solution of normal salts of the blood." Meanwhile, W. Reid Clanny (Case of Cholera at Sunderland with an Analysis of the Blood Taken from the Patient, *Lancet* **1**:505, 1831-1832) found that "in Elliot Todd [the patient] water, colouring matter and muriates of soda and potassa and carbonate of soda were respectively 644, 253 and 0 parts as against the findings in The Sailor [control] 756, 59, and 14 parts." The matter was soon pressed further (O'Shaughnessy, W. B.: Chemical Pathology of Cholera, *Lancet* **2**:225, 1831-1832; Clanny: Composition of Healthy and Cholera Blood, *Lancet* **2**:232, 1831-1832). However, the first practical application of the method seems to have been made by Thomas Latta, as reported in the abovementioned "Documents." Latta was stimulated by reading O'Shaughnessy's report on the blood in cholera. "The first subject of experiment was an aged female. She had apparently reached the last moments of her earthly existence, and now nothing could injure her. Having inserted a tube in the bacilic vein, cautiously—anxiously, I watched the effects; ounce after ounce was injected, but no visible change was produced. Still perservering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eyes, and fallen jaw, pale and cold, bearing the manifest imprint of death's signet, began to glow with returning animation, the pulse which had long ceased returned to the wrist; and in the short space of half an hour when six pints had been injected, she expressed in a firm voice that she was free of all uneasiness, actually became jocular, and fancied all she needed was a little sleep; her extremities were warm, and every feature bore the aspect of comfort and health." The patient soon became worse again and died; no further salt solution was injected.

Latta later worked out a formula—two or three drams of muriate of soda and two scruples of the subcarbonate in six pints of water, injected at temperature of 112 F. He

believed that often larger amounts must be given and attributed failure mainly to "too little and too late." A moribund woman was restored by injection of 330 ounces (9900 cc); "in 48 hours she smoked her pipe free from distemper" and proceeded to get well. "The apparatus I have used is Read's patent syringe, having a small silver tube attached to the extremity of the flexible injecting tube. The syringe must be quite perfect so as to avoid the risk of injecting air."

The report continues with abstracts of cases in which the saline therapy was used by Drs. Lewin, Craigie, Macintosh, and Racy. All agreed on the undoubted benefits of this form of treatment. We learn incidentally of the impunity with which unsterile solutions may be injected into the vein.

During the ensuing year there are more case reports in the *Lancet*, some favorable, some unfavorable, but with the subsidence of the epidemic this mode of therapy seems to have been neglected, although scattered case reports and notes are found through the years. The procedure did not ever become standardized, and as late as 1873 A. Netter (Des injections qui se pratiquent dans les veines des cholériques, et de la causes des variations des résultats obtenus jusqu'ici avec ce moyen thérapeutique, *Gaz. hôp. Paris* **46**:1107, 1873) analyzes the difficulties and uncertainties of the method, pointing out that while the immediate results are almost uniformly promising the later effects are variable. He analyzes the situation more at length in a little monograph (Netter, A.: Vues novelles sur le Cholera avec une étude sur les injections faites dans les veines, Paris, J.-B. Baillière et fils, 1874). The whole subject was later reviewed by Rogers (Ref. 19).

4. History of the Rise, Progress, Ravages, etc. of the Blue Cholera of India, Editorial, *Lancet* **1**: 241, 1831-1832.

With the recent outbreak of cholera in England the weekly medical journals for 1831-1832 are filled with notes, suggestions, and case reports of the disease. The present article of 43 pages gives an authoritative review of current knowledge. After a section on the origin and spread of epidemic cholera there is a vivid description of the symptomatology, emphasizing the vomiting and purging followed by muscle cramps, anuria, pulselessness, and the bluish shrunken appearance of the skin. As to pathology, emphasis is placed on the huge quantity of turbid fluid in the bowel with the deposit of immense amounts of "an argilaceous substance." Changes in the mucous membrane are also mentioned. "Every character of the cholera authorizes us in concluding, that it arises from failure of a portion of the *nervous system* [Bell]." The writers did however feel that cholera was communicable and quote the conclusions of Drs. Russell and Barry: "1. That the poison of cholera may be conveyed and communicated by man to man. 2. That like the poison of typhus, it is regenerated in great quantities by those who suffer its influence." The arguments against contagion are next summarized, and then there is a discussion of the confused irrational ideas on treatment which existed at the time.* It is of interest to read the arguments whereby almost everyone agreed on bleeding as the backbone of therapy. The article concludes with a discussion of sanitary measures, especially the quarantining of ships. There is no mention of contaminated water playing a part in contagion.

5. **Tardieu, A.** Du Choléra Épidémique, Paris, Germer Baillière, 1849.

These interesting lectures make clear that there had been no advance in understanding

* "The whole of Europe is little more than a vast advertisement, in which are announced, in colossal letters, the admirable recipes for the preservation against and the cure of this disorder. Here cincture is advised, there an elixir is lauded, and everywhere we meet abundant proof, that if this is the age of intelligence, knavery is not less on the increase. But even among men of the utmost science and purest intentions, equal diversity of sentiment prevails. One advocates venesection, while another as energetically cries it down. Sedatives and stimulants, emetics, cathartics and specifics, each have their strenuous supporters. It is worthy of remembrance too that these discussions are the fiercest among the actual witnesses of the disease."

of the disease since the studies in the epidemic of 1832. The usual atmospheric and telluric causes are discussed and as to contagion "we have seen the most ingenious theories, the most appealing, even for keen minds fall before an examination of the facts" (p. 148). As to treatment there are mentioned ipecac, Dover's powder, calomel, bismuth subnitrate, cubebs, ammonia, camphor, ether, oil of Cajeput, guaco, hashish, chloroform, as well as "the barbarous attempts at transfusion of blood or injection of water into the veins." One can see that intravenous therapy was making no progress.

The clinical descriptions are vivid, and there is an excellent section, as one might expect from the French, on the pathology of cholera.

6. Report of the [Boston] Committee of Internal Health on the Asiatic Cholera, Boston, I. H. Eastburn, 1849.

This careful report was issued as a result of the Boston epidemic of cholera in 1849. The major part of the book consists of detailed autopsy reports on 33 cases. No general conclusions are drawn, but in most of the cases the fluid material in the bowel and the changes in mucous membranes are stressed. "Examined by the microscope [the bowel contents] the flocculi, suspended in the rice-water fluid, invariably consisted of columnar epithelium. The epithelium-cells were so abundant and well-defined as to leave no doubt that they constituted nineteen-twentieths of the mass of the flocculi. If maceration, however, is the only cause of the separation of such an enormous quantity of epithelium, how shall we explain it in the situations where no increased amount of fluid has existed? The mucous surfaces of the vagina, and of the urinary bladder are invariably smeared with a thick whitish, pasty or creamy secretion, which on microscopic examination is seen to consist entirely of detached epithelium cells." (p. 47). Under treatment it is stated that narcotics "totally failed of any beneficial effect." The same was true of stimulants, emetics, calomel, quinia, tannic acid, ginger, cinnamon, and elaterium. Ether by inhalation relieved the cramps, but no one recovered who used it in this way. As to venous injection: "In one or two cases there was temporary relief, but death invariably followed shortly after. We were not inclined to make new trials of this mode of treatment after the first six weeks of the epidemic." The time was not yet ripe to use the method properly.

7. **Snow, J.** On the Mode of Communication of Cholera, London, J. Churchill, 1849.

Snow advanced the view that cholera was disseminated by something in the fecal discharges of patients which was later ingested by healthy people who thus acquired the disease. He stressed contaminated water supplies as the chief source. This was not a "study chair" piece of reasoning, but Snow was indefatigable in field work which seemed to support his views. However, he could not at first gain any attention. In the monumental "Report of Epidemic Cholera. Drawn up at the desire of the Cholera Committee of the Royal College of Surgeons by William Baly and William W. Gull, London, John Churchill, 1854," for example, six theories of causation are mentioned as possibilities. "The *Third* theory—that propounded by Dr. Snow—gives a more specific form to the doctrine of contagion. It supposes that the poison of cholera is swallowed, and acts directly on the mucous membrane of the intestines, is at the same time reproduced in the intestinal canal, and passes out, much increased with the discharges; and that these discharges afterwards, in various ways, but chiefly by becoming mixed with the drinking water in rivers or wells, reach the alimentary canals of other persons, and produce the like disease in them" (p. 5). But after several hundred pages of analysis the experts reject Snow's views: "Of the six theories, then, that alone is supported by a large amount of evidence which regards the cause of Cholera as a matter increasing by some process, whether chemical or organic, in im-

pure or damp air, and assumes that, although, of course, diffused with the air, it is also distributed and diffused by means of human intercourse" (p. 223). But Snow fought on, and on Jan. 21, 1854, for example, he spoke at the Medical Society of London as reported in the *Lancet* (1:109, 1854). There he laid out a rational method of therapy emphasizing "medicines which have the effect of destroying low forms of organized beings," to be given for their local effect and that "it was useless to attempt to bring the patient out of the state of collapse by stimulants and the application of heat, and they should be given watery drinks, unless in desperate cases, in which it might be desirable to inject into the blood vessels a weak saline solution, resembling that portion of the blood which has been lost." The reporter continues: "Indeed, if a layman had been present at the meeting, he might have witnessed a remarkable illustration in the way in which 'doctors differ,' and surely his faith in physic would have been scarcely increased in strength. Every speaker seemed to have an opinion of his own on the subject of the nature and cause of the disease. The treatment was no less contradictory." Snow continued, however, to collect evidence in support of his views and in 1855 published a "Second Edition, much Enlarged" of his book, which embodies the contents of numerous papers published in the contemporary medical journals. This second edition has been reproduced as a belated tribute to Dr. Snow, in facsimile (Snow on Cholera, Being a Reprint of Two Papers by John Snow, M.D., New York, The Commonwealth Fund, 1936). Snow did for cholera what Budd did for typhoid fever, and his work is required reading for all interested in the subject.

8. **Pettenkoffer, M.** Untersuchungen und Beobachtungen über die Verbreitungsart der Cholera nebst Betrachtungen über Massregeln derselben ein Halt zu thun, München, J. G. Cotta, 1855.

This book, the work of Pettenkoffer, the famous hygienist, is based on meticulous observations on the cholera outbreak in Bavaria in 1854-1855. Pettenkoffer's work consisted of careful study of the details of the epidemic and is definitely modern in tone. By studying spot maps of the location of cases in Munich and elsewhere he convinced himself that contaminated water had nothing to do with the spread of cholera. He was sure, however, that the disease was communicable; he believed that the agent was present in urine and stools, and he consequently developed an elaborate system of disinfection. By 1875 Pettenkoffer had not changed his views a great deal (Künftige Prophylaxis gegen Cholera, besprochen von Max v. Pettenkoffer, München, Th. Riedel, 1875). He believed there was a specific cholera germ which occurred principally in the stools but that its transmission was bound up with certain special conditions of the soil and ground water. He still laid stress on disinfection of stools and everything else the cholera patient came in contact with.

9. **Fauvel, A.** Le Choléra, Étiologie et prophylaxie etc., exposé des travaux de la Conférence Sanitaire Internationale de Constantinople, Paris, J.-B. Baillière et Fils, 1868.

By the time of the epidemic of 1865-1866 opinion had swung strongly to the view that cholera was contagious. As to the nature of the "materies morbi" and the mode of its propagation there was, however, great dispute. Innumerable books and articles were published, of which we may mention as examples that of Bernard M. Byrne (An Essay to Prove the Contagious Character of the Malignant Cholera, Ed. 2, Philadelphia, Childs & Peterson, 1855) as well as "A Communication from the City Physician on the Asiatic Cholera: Is it a contagious disease? City of Boston, City Document No. 21, 1866." Of great importance however is the "Report to the International Sanitary Conference." This body, consisting of 21 physicians representing various nations, was sent by the French Government to Egypt at the start of the epidemic of 1865 "to study the progress of the disease, its march and its

special character, with a view to arresting its onward movement." This valuable document of some 100 pages takes up the subject of cholera as a series of 33 questions which are discussed, analyzed, and voted on by the members of the commission for acceptance or rejection. The commission accepted unanimously the proposition that cholera is propagated by man and is transmissible. They concluded, however, that the principal mode of transmission was by emanation into the air, although water and certain ingesta may also serve as vehicles for the introduction into the organism of the generative principle of cholera through the respiratory passages and very probably also the digestive canal. The germ, however, was mainly in the dejecta and took its origin probably in the digestive canal. They thought that the "germ" could only be transmitted during the first few days of the disease. Many other questions are discussed. This document is especially important as representing the carefully considered views of a large group of top-flight physicians and scientists. An abstract of the report appeared in the *Boston Medical and Surgical Journal* (**75**:42, 1866), and an English translation of part of the full report appeared in Boston in 1867.†

10. **Hirsch, A.** Handbuch der historisch-geographischen Patholgie: Indische Cholera, Ed. 2, Stuttgart, Ferdinand Emke, 1881, Vol. 1, p. 279. [Hirsch, A.: Handbook of Geographical and Historical Pathology, English translation by Charles Creighton, M.D., London, The New Sydenham Society, 1883, Vol. 1, p. 394.]

Much of the literature on cholera is concerned with epidemiology and descriptions of outbreaks. This is the classical storehouse of information to date. Various epidemics all over the world are listed and documented. For more recent lists of outbreaks see Carle Mense: Handbuch der Tropenkrankheiten, Ed. 2, Leipsic, Barth, 1914, Vol. 3, p. 243 et seq.; H. Harold Scott: A History of Tropical Medicine, Baltimore, The Williams & Wilkins Company, 1939, Vol. 2, p. 663 et seq.; and Sir Leonard Rogers: Bowel Disease in the Tropics, London, Henry Frowde, 1921, Ch. 1, p. 1 et seq. C. Macnamara's "A History of Asiatic Cholera," London, Macmillan & Company, 1876, may also be consulted.

11. Conferenz zur Erörterung der Cholerafrage. Verhandelt Berlin, im Reichsgesundheitamt, am 26. Juli 1884. Abends 6 Uhr. *Berlin, klin. Wchnschr.* **21**: 477; 493, 1884. [English translation of Koch's remarks, *Brit. M. J.* **2**: 403; 453, 1884.]

Koch tells how he went to Egypt to study cholera. After doing many autopsies he convinced himself that the only plausible place to seek the germ was in the intestines. The changes were all the way from very slight to reddening and swelling of Peyer's patches to a necrosis of the mucosa with a diphtheritic covering. On sections it was found that the space between epithelium and basement membranes of glands was crowded with numerous comma-shaped bacilli. These were also found in the intestinal contents. The organisms and their cultural characteristics are described in detail. Koch found that the organism was short-lived and did not survive when dried on clothes or in soil. He found the comma bacillus in the dejecta of numerous cholera cases in almost pure culture. "In accordance with the cholera-material that I have so far examined, I think I can now assert that comma-bacilli are never found absent in cases of cholera; they are something that is specific to cholera." In patients with other diseases the comma bacilli were never found, nor were they obtained from two men who had cholera, respectively, six weeks and eight days previously. Koch recognized, however, that

† Report to the International Sanitary Conference, of a Commission from That Body, to Which Were Referred the Questions Relative to the Origin, Endemicity, Transmissibility, and Propagation of Asaiatic Cholera, translated by Samuel L. Abbot, M.D., Boston, Alfred Mudge & Sons, 1867.

further proof was necessary of the causal role of the bacillus, and he fed numerous small animals with fresh dejecta and with cultures. All remained well. He observed, however, that several laundresses who handled cholera linen came down; this he accepted as strong evidence. "If, therefore, an infection can be brought about by cholera-linen, then, as the comma-bacilli are the only micro-organisms in question, it can only be brought about by them." He asks how an organism confined to the intestine can make a person so ill and suggests that the organisms produce soluble absorbable toxins. He recovered comma bacilli from a large tank in which a number of people did their washing and from which they also drank the water. He thought water and moist food the commonest ways of infection; dried material was a less likely source. Koch points out that the same person is rarely affected twice in the same epidemic; he concludes, therefore, that the disease is followed by a temporary immunity. Finally, he hopes that the discovery of the cholera bacillus will be of use in diagnosis and therapy.

The article, like Koch's work on the tubercle bacillus, seems complete and unassailable; it should be carefully studied by all interested in the subject.

In another paper (Koch, R.: I. Über die Cholerabacterien, *Deutsche med. Wchnschr.* **10**:725, 1884) he discusses the subject further and answers certain objections made by others.

Koch does not mention dehydration and salt loss as a feature of this disease.

Koch went to India and confirmed the results he had obtained in Egypt. As with every important bacteriological discovery, there were some who doubted and some who obtained contradictory results. In another communication (Further Researches on Cholera, *Brit. M. J.* **1**:6, 1886) Koch systematically answers (and demolishes) his opponents. He also discusses animal experiments, and he thought he produced cholera in guinea-pigs.

12. Pfeiffer, R. Untersuchungen über das Choleragift, *Ztschr. Hyg. u. Infectionskr.* **11**: 393, 1892.

The cholera bacillus was discovered during the lush flourishing of the bacteriological era. Everyone looked to immunological methods of diagnosis, protection, and therapy. There was immediate great debate about cholera bacilli as to whether they remained in the intestine and secreted a soluble exotoxin or whether in process of disintegration they yielded poisonous endotoxin. Pfeiffer made pioneer experiments to try to answer this problem, injecting small animals with broth cultures, with bacteria-free filtrates, and with living and dead bacteria. "In young aerobic cholera cultures there is a specific poison which displays extraordinary intense toxic action. This primary cholera poison is very closely related to the bacterial bodies and is perhaps an integral part of them." Pfeiffer later (Studien zur Choleraätiologie, *Ztschr. Hyg. u. Infectionskr.* **16**:268, 1894) elaborated these ideas. He produced immune sera in guinea pigs of which "very small amounts are adequate to confer on guinea pigs pronounced protection against intraperitoneal injection of cholera virus." Issaeff (Untersuchungen über die Künstliche Immunität gegen Cholera, *Ztschr. Hyg. u. Infectionskr.* **16**:287, 1894) confirmed Pfeiffer's work and showed that serum of human convalescents from cholera had high protective qualities against the bacteria but not against the endotoxins of the vibrios.

13. Wassermann, A. Untersuchungen über Immunität gegen Cholera asiatica, *Ztschr. Hyg. u. Infectionskr.* **14**:35, 1893.

Although empirical attempts at human immunization against cholera had already been made by Ferrán (Ref. 16), it remained for the German workers to lay the experimental background. In the present paper the writer showed: "It is definitely possible to protect guinea pigs against the intraperitoneal infection with living cholera bacilli. In order to achieve this one must inject cholera vibrios

or their body substance in such doses that a mild specific illness, a general reaction follows." R. Pfeiffer and A. Wassermann (Untersuchungen über das Wesen der Choleraimmunität, *Ztschr. Hyg. u. Infectionskr.* **14**:46, 1893) continued this work and emphasized the need of a clear experimental foundation before human beings were treated.

14. Koch, R. Wasserfiltration und cholera, *Ztschr. Hyg. u. Infectionskr.* **14**:393, 1893.

In 1892 occurred the famous cholera epidemic affecting especially Hamburg, which was supplied with unfiltered water from the river Elbe, whereas the adjacent cities of Altona and Wandsbeck, which differed only in having a filtered water supply, had practically no cases of the disease. Koch discusses this situation in detail and draws the inevitable conclusions as to the epidemiology of cholera. Koch pursues the matter further (Die Cholera in Deutschland während des Winters 1892 bis 1893, *Ztschr. Hyg. u. Infectionskr.* **15**:89, 1893) in a long and interesting article.

15. Pfeiffer, R., and Issaeff. Über die specifische Bedeutung der Choleraimmunität, *Ztschr. Hyg. u. Infectionskr.* **17**:355, 1894.

This is the classical paper in which was described what was later known in immunology as the "Pfeiffer phenomenon." The authors showed that cholera vibrios injected into the peritoneum of an immune guinea-pig underwent rapid dissolution; if another organism was injected or if the guinea-pig was nonimmune the injected bacteria were unaffected. Pfeiffer, therefore, made an important contribution to the knowledge of cholera and discovered a general immunological principle as well. The protection turned out to be purely antibacterial, as the animals were still just as sensitive to cholera "toxin." Pfeiffer later (Weitere Untersuchungen über der Choleraimmunität und specifisch bactericide Processe, *Ztschr. Hyg. u. Infectionskr.* **18**:1, 1894) restated his principle "that the serum of animals which are actually immunized against cholera only shows a specific action against the vibrios whereas against other bacteria it behaves no differently than the serum of normal animals." In this elaborate paper he gives the details of further studies with vibrios and "toxin" in rabbits and guinea pigs. Pfeiffer assumed that his reaction could take place only in the animal body, but Metchnikoff (Metchnikoff, E.: Études sur l'immunité: Sixième memoire. Sur la destruction extracellulaire des bactères dans organisme, *Ann. Inst. Pasteur* **9**:369, 1895) soon demonstrated extracellular lysis in hanging drop preparations.

16. Haffkine, W. M. Anti-Cholera Inoculation: Report to the Government of India, Calcutta, Thacker & Spink, 1805. [See also Haffkine, W. M.: Protective Inoculation Against Cholera, London, W. Thacker & Company, 1913.]

Ferrán in 1885 (Ferrán, J.: Nota sobre una vacuna química contra el cólera asiático, *Rev. cien. méd., Barcelona* **11**:515, 1885) was apparently the first worker who claimed to produce immunity against cholera by subcutaneous injection of cholera bacilli. In another note (Sur la Prophylaxie du choléra au moyen d'injections hypodermiques de cultures pures du bacille-virgule, *Compt. rend. Acad. sc.* **101**:147, 1885) Ferrán describes his method, which consisted simply of subcutaneous injections at five-day intervals of three doses of a living broth culture of the bacilli. "I affirm to the Academy that the manner of abruptly interrupting the curve of mortality of an epidemic of cholera has today been accomplished by science." Ferrán does not however give any actual protocols, and his work seems to have been questioned at the time. A little later W. M. Haffkine (Le Choléra asiatique chez le cobaye, *Compt. rend. Soc. biol.* **4**:635, 1892) succeeded with injections of attenuated live cholera bacilli in rendering guinea pigs immune. "An animal having been vaccinated first with attenuated and then with 'exalted' virus is protected against every infection with cholera no

matter how one tries to produce it." He soon (Le Choléra asiatique chez le lapin et chez le pigeon, *Compt. rend. Soc. biol.* **4:** 671, 1892) reported the same findings with rabbits, and finally he showed that man could be safely injected with living cholera bacilli (Inoculations de vaccines anticholériques à l'homme, *Compt. rend. Soc. biol.* **4:**740, 1892). E. H. Hankin (Remarks on Haffkine's Method of Protective Inoculation Against Cholera, *Brit. M. J.* **2:**569, 1892) submitted himself to inoculation by Haffkine and describes his own febrile and local reactions. "The evidence shows that M. Haffkine's method of inoculation is not attended by any grave disturbance of health, and that it can be practiced on human beings with perfect safety." A little later A. E. Wright and D. Bruch (On Haffkine's Method of Vaccination Against Asiatic Cholera *Brit. M. J.* **1:***227*, 1893) described in detail the method of preparing the attenuated form of vaccine by treatment with phenol and the exalted form by guinea pig passage. Their carbolized vaccine contained no live bacilli. The seat of election is injection under the skin of the flank, the first (attenuated) vaccine being given three to five days before the second (exalted) preparation.

Haffkine later went to India, where he used his method extensively under the sponsorship of the British and wrote his elaborate report to the Government. Haffkine believed that the vaccine was effective, although the detailed figures are not very impressive. He states very conservatively, however: "The results obtained seem to indicate that in the inoculation we possess a means of effectively combating cholera epidemics. I am of the opinion that this experimental stage is not yet in that advanced condition to be completely closed" (p. 47).

W. Kolle (Zur activen Immunisierung des Menschen gegen Cholera, *Centralbl. Bakt.* **19:**97, 1896) was another pioneer in anticholera immunization. In this important article he gives a valuable review of the theoretical basis for anticholera vaccination and quotes the fundamental experiments on which this is based. In practice he injected, first, chloroform-killed bacteria and 5 and 10 days later live virulent vibrios. Later he seems to have changed the vaccine to a culture killed by heating to 58 C for one hour and preserved with 0.5% phenol (P. Krause and T. Rumpf, in Mense, C.: Handbuch der Tropenkrankheiten, Ed. 2, Leipsic, Barth, 1914, Vol. 3, p. 299). This is essentially the type of vaccine used at present by the United States Army.

M. L. Ahuja and Gurkirpal Singh (Observations on Cholera Vaccine, *Indian J. M. Res.* **36:**1, 1948) give experimental support for the use of a mixture of Inaba and Ogawa strains in preparing the vaccine.

The results of anticholera inoculation have, however, been variously judged. Major Greenwood and G. Udney Yule (The Statistics of Anti-Typhoid and Anti-Cholera Inoculations, and the Interpretation of Such Statistics in General, *Proc. Roy. Soc. Med., Sec. Epidemiol. & State Med.* **8:**113, 1915), for example, expert statisticians, give a careful mathematical analysis of published results. While somewhat reserved, Major Greenwood says in conclusion that "so far as the data went, the case in favour of anti-cholera inoculation seemed to them strong."

R. Adiseshan, C. G. Pandit, and K. V. Venkatraman (Statistical Evaluation of Anti-Cholera Inoculation as a Personal Prophylactic Against Cholera and Its Efficiency in the Prevention and Control of Cholera Epidemics, *Indian J. M. Res.* **35:**131, 1947) found that the case incidence in 709,977 vaccinated persons was 1.57%; in 2,119,568 unvaccinated it was 16.20%. They thought that protection lasted for a minimum period of six months. The vaccine contained both Inaba and Ogawa subtypes of Vibrio comma and was given in one dose of 8,000,000 organisms. Quite recently L. Kant (An Assessment of the Value of Cholera Vaccine as Used in a Single Dose Mass Inoculation [a Field Observation], *J. Trop. Med.* **54:** 223, 1951), in an observation covering 30,683 persons in India, reaffirmed the protective action of the vaccine.

17. Gotschlich, F. Über Cholera und choleraähnliche Vibrionen unter den aus Mekka zurückkehrenden Pilgern, *Ztschr. Hyg. u. Infectionskr.* **53**:281, 1906.

Sooner or later it was inevitable that vibrios resembling those specific for cholera would be found. Gotschlich working at the quarantine station at El Tor examined the intestinal content of 107 pilgrims dead of various forms of dysentery or colitis, but not of cholera, in which he found vibrios in 38 cases. Many of these strains were agglutinated in high titer in anticholera sera, but they were actively hemolytic and differed in certain other respects from the cholera vibrios. The problem is fully discussed by Linton (Ref. 22). At any rate, it is established that vibrios resembling those of cholera but harmless or causing other bowel disturbances exist not infrequently.

18. Kolle, W. Zur Frage der Serumtherapie der Cholera asiatica, *Deutsche med. Wchnschr.* **35**:2046, 1909.

Since serum therapy has in the end been abandoned in cholera we shall not attempt any lengthy bibliography. However, serum therapy had an active vogue at the turn of the century, and so it should not be entirely ignored. Kolle's paper is a summary of the whole situation by an authority in the field. He points out that the great difficulty is that cholera patients die of "intoxication" and not of bacterial invasion, whereas immune serum is essentially antibacterial. He reports a death rate of 37.5% in serum-treated cases of severe cholera and in general is conservative in his predictions of the future of cholera immunotherapy.

19. Rogers, L. The Treatment of Cholera by Injections of Hypertonic Saline Solutions with a Simple and Rapid Method of Intraabdominal Administration, *Phillippine J. Sc.* **4**:99, 1909.

We have already reviewed the early efforts at intravenous saline therapy in cholera (Ref. 3). Even in modern times it was variously judged. Rogers (Recent Advances in Tropical Medicine, Ed. 2, Philadelphia, P. Blakiston's Sons, 1929, p. 192) cites death rates of from 59% to 70%. Henry J. Nichols and Vernon L. Andrews (The Treatment of Asiatic Cholera During the Recent Epidemic, *Philippine J. Sc.* **4**:81, 1909), on the other hand, felt that they reduced the death rate to 20% to 40% by intravenous infusions of 0.85% salt solution. Rogers, however, not having had good final results with isotonic saline, concluded that salt was lost out of proportion to fluid and therefore doubled the strength of his solution. "On rapidly increasing the strength to double that formerly used (2 drachms of sodium chloride to the pint, or 1.35 per cent, to which 3 grams of calcium chloride may be added) a most gratifying degree of success was obtained." The mortality was reduced from 61% to 32.5%. He calculated the amount of solution to be given by "estimating the percentages of serum and corpuscles with the haemocrite." Rogers, later (A Simple Curative Treatment of Cholera, *Brit. M. J.* **2**:835, 1910), discussed the treatment further and added to the saline injections internal administration of potassium permanganate to destroy "the specific toxins within the alimentary tract." He felt he increased the recovery rate sevenfold. The idea of using salt solution more concentrated than isotonic saline was not, however, new when Rogers applied it. Much earlier G. Gaertner and A. Beck (Über den Enfluss der intravenosen Kochsalzeinspritzung auf die Resorption vom Flussigkeiten, *Wien. klin. Wchnschr.* **6**: 563, 1893) laid down the principles of the subject and advocated concentrated salt solution in cholera as rational to check the immense transudation of fluid into the bowel. A. W. Sellards (Tolerance for Alkalies in Asiatic Cholera, *Philippine J. Sc.* **5**:363, 1910) emphasized the acidosis (increased tolerance for alkali) in cholera patients, especially those who were anuric, and he pushed the intravenous injection of solutions of sodium bicarbonate with what he thought were good therapeutic results. In the light of modern studies of electrolytes and fluid

balance it is difficult to evaluate this procedure. Yet up to the present time intravenous fluids in some form remain the backbone of the treatment of cholera.

20. Goodpasture, E. W. Histopathology of the Intestine in Cholera, *Philippine J. Sc.* **22**:413, 1923.

Goodpasture made definitive studies of the histology of the intestine in cholera. He found that one must have absolutely fresh material to avoid rapid postmortem changes. He concluded that desquamation of epithelium was for the most part a postmortem change but that antemortem desquamation might occur, recognizable at autopsy by the presence of ulcers with acute inflammatory exudate. "Anatomical evidence indicates that the great mass of vibrios is confined to the intestinal lumen, and, if toxic substances are formed there directly or indirectly as a result of their growth, they are absorbed early in the disease through an anatomically intact mucosa."

21. [Couvy]. Rapport sur les porteurs de germes de choléra, *Bull. mensuel, Office internat. d'hyg. publique, Paris,* **25**:1149, 1933.

W. Kolle first showed years ago (Über die Dauer des Vorkommens von Choleravibrionen in den Dejection von Cholerareconvalescenten, *Ztschr. Hyg. u. Infectionskr.* **18**:42, 1894) with daily cultures in 50 convalescents that the vibrios in all but 1 case disappeared in from 3 to 28 days.

Couvy recognizes the discharge of cholera vibrios by those in the incubation period or during convalescence but doubts the occurrence of chronic "healthy" carriers. Probably some of the incriminated did not carry true pathogenic cholera vibrios. At any rate, the "chronic carrier" seems to play an insignificant part in the epidemiology of the disease. This comprehensive report includes elaborate statistics from the literature. The rarity of the persistence of the vibrios in convalescents is also brought out by the report of Y. Y. Ying (The Persistence of Vibrios in Cholera Patients, *Chinese M. J.* **58**:595, 1940), who found in 200 cases of proved cholera "A large proportion of cases (76.5%) show positive stool cultures during the first week followed by a rapid decline thereafter, being 21.5% for the second, 1.5% for the third and 0.5% for the fourth week. Not a single case showed a positive culture after the fourth week."

22. Linton, R. W. The Chemistry and Serology of the Vibrios, *Bact. Rev.* **4**:261, 1940.

As is usually the case, the simple ideas of the early investigators in bacteriology have been displaced by highly complicated chemical and physical studies. It is outside the scope of this bibliography to review the subject in detail, but this comprehensive summary goes into the chemical structure of vibrios, their growth products, their metabolism and chemical classification, their antigenic structure, etc. The problems raised years ago by Pfeiffer (Ref. 15) and others are not yet fully solved.

23. Felsenfeld, O.; Dadtraday, W. S.; Sacheko, J. I.; Thorn, W., and Norsen, J. In Vitro Sensitivity of Recently Isolated Cholera Vibrios to 10 Antibiotics, *Proc. Soc. Exper. Biol. & Med.* **77**:287, 1951.

With the advent of the newer antibotics it was inevitable that they should be tried against cholera. The present writers tested action of 10 commonly used antibiotics against 53 recently isolated strains of V. comma. "The results showed a wide variation in susceptibility to these drugs according to the geographical origin of the vibrios." In a preliminary trial S. C. Seal, S. C. Ghosal, and M. M. Ghosh (A Preliminary Trial of Aureomycin [I. V.] in the Treatment of Cholera, *Indian M. Gaz.* **86**:287, 1951) found that in clinical use "no therapeutic advantage has been demonstrated." A. Das, S. Ghosal, S. K. Gupta, and R. N. Chandhuri (Terramycin in Cholera, *Indian M. Gaz.* **86**:436, 1951), in a somewhat more

extensive trial, found also that oxytetracycline (Terramycin) made no significant difference in the effects of treatment. Similar results were obtained by N. R. Koner and A. N. Sengupta (Terramycin in Cholera, *Indian M. Gaz.* **83**:469, 1951), although they found that the first negative report of stool culture was obtained earlier in oxytetracycline-treated cases. On the other hand, E. Olejnik and S. Davidovitch (Action of Terramycin and Chloromycetin on Cholera Vibrio in Mice, *Nature, London* **168**:654, 1951) found that mice inoculated intraperitoneally with V. comma could be saved by both oxytetracycline and chloramphenicol, provided the drug was given within five hours after infection. S. C. Lahin (Chemotherapy in Cholera, *Brit. M. J.* **1**:500, 1951) tried sulfaguanidine and other sulfonamides in cholera without reducing the mortality rate.

The subject of antibiotics in cholera is treated editorially in the *Journal of the Indian Medical Association* (**22**:291, 1953), and the writer concludes "The failure of these vibriocidal drugs once more emphasizes the immense importance both of prophylaxis and of the early restoration of body fluids on sound biochemical principles."

Apparently cholera comes like a storm and is quickly over, and the main therapeutic measure remains the restoration of fluid and salts.

24. Ahuya, M. L.; Krishnan, K. V.; Pandit, S. R., and Venkataraman, K. V. Laboratory Diagnosis of Cholera, *Indian J. M. Res.* **39**:135, 1951.

Koch (Ref. 11) laid the foundation of laboratory diagnosis of cholera. The present note is an up-to-date statement of the best bacteriological procedure for isolating and identifying the cholera vibrio.

Pulmonary Apical Herniations

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The gradual appearance of a soft bulging prominence in one or both supraclavicular areas sometimes arouses a patient's apprehension. On examination, this bulge is neither indurated nor tender, and no definite mass can be palpated. When the patient coughs, strains or performs the Valsalva maneuver, the swelling expands considerably and a gentle outward positive impulse becomes perceptible. The bulging is usually symmetric but occasionally is unequal. A history of chronic cough for many years often is elicted, and many of these patients are emphysematous. This soft expansile mass is actually due to increased protrusion of the lung through the superior thoracic aperture, and is regarded as pulmonary apical herniation.

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In our experience supraclavicular herniation of the lung is not unusual. Nineteen cases seen recently are reported here (Table). Nevertheless, references to this condition in the literature are meager, consisting mainly of individual case reports. Until 1946 only 185 cases had been collected by Maurer and Blades,[1] mostly of traumatic origin. Meakins, Wyatt, and Aronovitch [2] reported two cases of right cervical hernia, both occurring in male patients many years after severe trauma to the neck. Van Wezel [3] recorded the case of a man of 39 with a right cervical hernia occurring after six years of severe coughing. Reinhart and Hermel [4] observed two male patients in the fifth decade, each with a right cervical hernia, associated in one with a chronic cough. Banyai [5] recently

Data on Patients with Pulmonary Apical Herniation

Case No.	Patient	Age, Yr.	Sex	Clinical Diagnosis	Supraclavicular Prominence, at Rest*	Supraclavicular Prominence During Cough or Strain*	
						Right	Left
1	H. W.	57	M	Chronic bronchitis and emphysema	0	+++	+++
2	F. K.	73	F	Chronic bronchitis and emphysema	+	+++	+++
3	I. D.	60	F	Chronic bronchitis and emphysema	0	+	+++
4	P. S.	74	F	Chronic bronchitis and emphysema	0	+++	+++
5	H. K.	83	M	Chronic bronchitis and emphysema	0	+++	+++
6	M. P.	66	M	Chronic bronchitis and emphysema	0	+++	+++
7	E. K.	74	M	Chronic bronchitis and emphysema	0	+++	+++
8	A. S.	74	M	Chronic bronchitis and emphysema	0	+++	+++
9	A. R.	55	M	Chronic bronchitis and emphysema	0	++	++
10	I. C.	80	M	Chronic bronchitis and emphysema	0	++++	+++
11	A. S.	84	F	Chronic bronchitis and emphysema	0	+++	+
12	R. L.	84	F	Asthma and emphysema	0	+++	+++
13	H. G.	74	M	Emphysema	0	+++	+++
14	E. A.	54	F	Emphysema	+	+++	+++
15	M. S.	63	F	Emphysema	+	+++	++
16	H. B.	59	M	Emphysema	+	++++	++++
17	P. B.	65	F	Emphysema, bronchiectasis	+	+++	+++
18	G. W.	46	F	Arthritis	0	++	++
19	E. W.	45	F	Neurosis	0	++	++
20	I. K.	74	M	Fibroid pulmonary tuberculosis, emphysema	0	0	0

* 0 indicates no supraclavicular swelling, while + indicates some swelling and + to ++++ denotes the extent of the supraclavicular expansion, after strain either by coughing or with the Valsalva maneuver.

included cervical hernia as one of the harmful sequelae of coughing. Falliers [6] reported a case in a 4½-year-old girl who had a cough for two years, attributing the hernia to congenital weakness of Sibson's fascia aggravated by chronic cough. Palazzo and Garrett [7] described a bilateral hernia of the lungs in a 48-day-old infant, presumably of congenital origin.

ANATOMY AND PHYSIOLOGY OF THE SUPERIOR THORACIC APERATURE

The superior aperture of the thorax is enclosed by the first rib on either side. The apex of each lung rises 2 to 5 cm. above this opening. Superiorly and medially expansion is limited by the pleura and the deep cervical fascia (Sibson's fascia). Anteriorly, the cupolas rise above the clavicles and are restrained from protruding by the thin platysma and the medial portion of the sternocleidomastoid muscle. Laterally, however, they are protected by the three scalene muscles, and posteriorly, by the scapulae and trapezius muscles. Anatomically abnormal protrusion of the apex of the lung may therefore manifest itself in superior, medial, and anterior directions.

The cervical portion of the trachea anteriorly is unprotected by heavy musculature and is readily affected by increased pressure within its lumen. Posteriorly the tracheal cartilaginous rings are discontinuous, but the trachea is supported by the vertebral column and its overlying soft tissues.

In forced expiration with a partly closed glottis as in coughing, or with a completely closed glottis as in straining, a considerable pressure is exerted on the inflated lungs. This is produced by the increased abdominal pressure transmitted through the diaphragm by the contracting abdominal muscles, as well as by the pressure of the thoracic walls. This suddenly increased intrapulmonary pressure is transmitted to the cupola of each lung, which then protrudes medially and anteriorly towards the soft areolar tissue just above the manubrium and surrounding the trachea. If the cough is vigorous, some lateral expansion may be noticed as far as the sternocleidomastoid muscle. Moreover, as shown by our roentgenograms, when the trachea in the neck is subjected to this increased positive pressure, it expands and buckles. The jugular and subclavian veins and their tributaries become distended during this process, since their return flow is blocked by the positive intrathoracic pressure, and this too contributes to the swelling. Contracting cervical muscles also influence the bulging at the base of the neck during strain. These mechanics explain why a man's collar button is sometimes torn off during a vigorous cough or sneeze.

Fig. 1.—Lateral neck roentgenograms of a tall thin male patient showing the pulmonary apices (white arrows) protruding upwards into the supraclavicular fossae. This patient was a normal person who had been injured a few hours before.

CLINICAL FEATURES

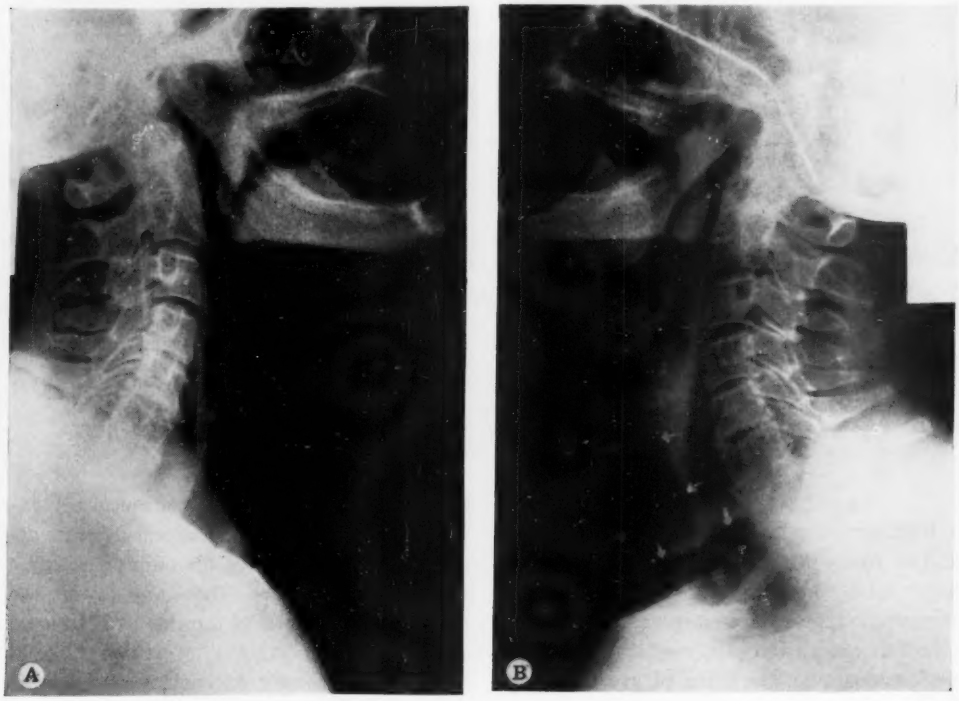
In the 19 patients reported here with pulmonary apical herniation (Table), the superior and lateral expansion at times has

extended almost to the acromioclavicular joint. In these persons, who were mostly adults with emphysema, the deep cervical fascia (Sibson's fascia) had probably become stretched after years of chronic cough so that the cupolas of the lungs protruded further into the neck when subjected to increased positive pressure. In some patients, part of this abnormal protrusion became permanent, and prominent supraclavicular swelling was evident even at rest. It is possible that the emphysema which affected most of our patients also contributed to the weak thoracic ceiling by widening the superior aperture because of elevation of the first rib.

Of our 19 patients, 10 were women. Their ages varied from 45 to 84 years, the average being 66 years. All but two were emphysematous, and all except four presented a history of a chronic cough for many years. The latter four patients had emphysema without pulmonary symptoms. In 12 patients the emphysema was associated with chronic bronchitis or bronchiectasis, and in one the emphysema was a sequel of 40 years of bronchial asthma. Five patients presented a supraclavicular bulge before coughing or executing the Valsalva maneuver, and the expansion became much greater after either procedure. In three patients the herniation was greater on the right side, and in one patient the left side protruded more. In the remainder the herniation was symmetric. Several patients admitted suffering from a chronic cough for years only after supraclavicular expansion had been detected by the examiner.

In one patient, Case 20, suffering from a chronic cough and found to have emphysema with extensive bilateral apical fibrosis of tuberculous origin, no supraclavicular expansion could be elicited. Evidently in this patient the fibrosis restrained the cupolas of both lungs.

Fig. 2.—*A*, lateral neck roentgenogram of a short stocky emphysematous patient at rest. There is no intrusion of the pulmonary apices into the supraclavicular fossae. *B*, same patient as in Figure 2*A*, during the Valsalva maneuver. The pulmonary apices project into the supraclavicular fossae (vertical arrows). Note the dilation of the trachea during strain (horizontal arrows).



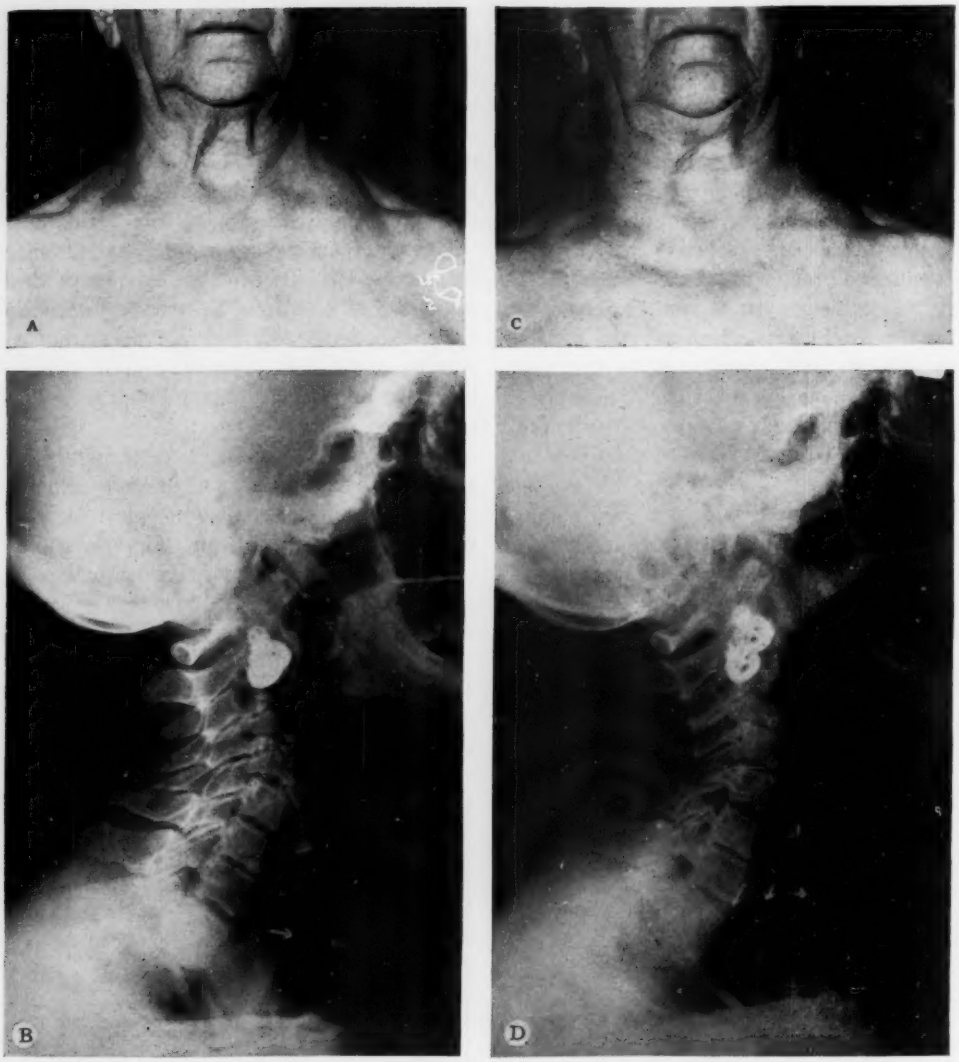


Fig. 3A.—Photograph of an emphysematous patient with bulging of the pulmonary apices into the supraclavicular fossae.

Fig. 3B.—Same case as Figure 3A at rest. The pulmonary apices protrude upward. The trachea (horizontal arrows) is normal.

Fig. 3C.—Same case as Figures 3A and 3B, photograph of supraclavicular fossas during the Valsalva maneuver. Note the increased prominences in the supraclavicular fossas.

Fig. 3D.—Same case as Figures 3A, 3B, and 3C. Note the anterior buckling of the trachea (horizontal arrows) and the increase in apical herniation (vertical arrows).

RADIOLOGICAL FEATURES

Radiographic studies on normal patients and on many of the emphysematous patients were made by means of posteroanterior teleroentgenograms in inspiration and expiration, apical lordotic views, and lateral neck exposures. The films of greatest diagnostic value for demonstrating apical herniation were found to be the lateral neck roentgenograms. These were the only ones which clearly demonstrated the cupolas of the lungs above the level of the clavicles. In none of the other projections were we able to visualize pulmonary parenchyma projecting

into the supraclavicular fossae. Therefore our data are based mainly on lateral cervical roentgenograms made at rest, midway in inspiration, and in exactly the same position after deep inspiration followed by forced expiration against the closed glottis with the nostrils blocked, the classical Valsalva maneuver.

In normal persons the upward extent of the lung apices into the supraclavicular fossae was found to vary with body habitus. In long thin patients a visible cupola may be demonstrated on lateral neck (Figure 1) roentgenograms even at rest, while in those with short necks and heavy chests the lung apices are rarely seen on lateral neck films. In normal patients of all body types no increase in the amount of lung tissue projecting into the supraclavicular fossae could be demonstrated during the Valsalva maneuver. In those in whom the apices were seen at rest, no further protrusion was elicited by straining.

At rest the cervical trachea is readily demonstrated on lateral neck roentgenograms as a tubular structure of uniform caliber. With the Valsalva experiment there is some increase in the anteroposterior diameter of the trachea as the air pressure mounts, with a tendency to slight forward buckling if the pressure is sustained for a few moments.

Comparative roentgenologic observations of the trachea and supraclavicular fossae were made at rest and during the Valsalva maneuver in eight of the patients listed in the Table. The roentgenograms at rest showed slight or no apical protrusion into the supraclavicular fossae and normal tracheas. With strain, however, the pulmonary apices assumed a prominent supraclavicular position as air-containing bulging shadows. This was variable and appeared to be related to the duration and force of the strain. In some instances the trachea was displaced anteriorly. The intracervical trachea dilated perceptibly and buckled anteriorly. The distention was particularly prominent in the posterior portion, where the cartilaginous rings become discontinuous (Figs. 2 and 3).

SUMMARY

In emphysematous patients, particularly those with chronic cough, pulmonary apical herniation is relatively frequent. It may be identified on physical examination by the presence of a soft painless supraclavicular bulge which is exaggerated by strain or cough. Radiologically this herniation can best be identified on lateral cervical roentgenograms.

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Tubeless Gastric Analysis

An Evaluation of Azure A Indicator Compound

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Several attempts have been made in the past to develop a simple yet accurate method for the detection of hydrochloric acid in the gastric content without intubation.* A quinine indicator resin proved to be useful for this purpose †; however, certain vitamins, steroids, and quinine-containing drinks or medication, by increasing urinary fluorescence, produced falsely high results; the rather troublesome and time-consuming extraction technique for the detection of quinine in the urine was an additional disadvantage.

The introduction of an azure A ion-exchange compound by Segal and coworkers [5] seemed to overcome the principal disadvantage of the quinine resin and to reflect the presence or absence of hydrochloric acid satisfactorily. The present report describes our experience with this compound as an index of the presence or absence of hydrochloric acid in the gastric content of 104 patients.

MATERIAL AND METHODS

The patients swallowed a Levin or Rehfuss tube and underwent the standard two-hour gastric analysis developed in our laboratory; those with established achlorhydria were not intubated. After the first hour, 3-(2-aminoethyl) pyrazole (gastramine; Histalog), 0.5 mg/kg. body weight, was injected subcutaneously as a secretory stimulant.[6] At the close of the second hour, the gastric tube was removed; the patients voided and then were given 2 mg. of azure A ion-exchange compound orally with 200 to 400 cc. of water. Urine specimens were collected during and exactly at the end of the subsequent first and second hours. The urine collections for the first hour and second hour test urines were diluted to 150 cc. Ten cubic centimeter aliquots of each were diluted with an equal volume of distilled water to give a concentration equal to that of 300 cc. dilution of the respective specimens. If any of the specimens exceeded 150 cc., proportionally less water was added to the 10 cc. specimens. Aliquots of the first- and second-hour test urines were proportionally mixed and diluted to a given azure A concentration corresponding to that of 300 cc. dilution of the two-hour total test urine. All specimens were acidified to between pH 1 and 2 and then were placed in a boiling water bath for 10 minutes to convert the colorless conjugated dye into blue azure A compound. The amount of azure A compound in the specimens was determined quantitatively with a Coleman Universal Spectrophotometer at a wave length of 620μ, 2 to 24 hours after cooling.

In all instances in which azure A compound was excreted, the second-hour specimens were uniformly clear blue after 10 minutes of heating and were best suited for visual comparison with standard solutions of azure A compound. On the other hand, the first-hour and the two-hour total test specimens usually appeared green or, on several occasions, cloudy gray. These turbid specimens were reexamined after the addition of a few crystals of aluminum chloride to a 10 cc. aliquot.‡ They then were diluted, acidified, and placed in a boiling water bath for 10 minutes. The supernatant fluid of the specimen after cooling became clear and was decanted for examination.

RESULTS

Of the 104 patients, 84 secreted hydrochloric acid during Histalog stimulation, the outputs ranging from 4.3 mg. to 1780 mg. in one hour. In one patient the urine was

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The azure A indicator compound was supplied by E. R. Squibb & Sons.

Department of Medicine, University of Chicago. United States Public Health Service Research Fellow of the National Cancer Institute (Dr. Galambos).

* References 1 and 2.

† References 3 and 4.

‡ Segal, H. L.: Personal communication to the authors.

TABLE 1.—*The Results of Azure A Test in 103 Subjects*

Gastric HCl	Mg. HCl in 1 Hr. of Gastric Secretion After Histalog Stimulation	Patients, No.	Azure A, Mg. In 2 Hr. Total Test Urine			In 2d Hr. Test Urine		
			Patients, No.	Range	Average	Patients, No.	Range	Average
Present	Under 50	5	3*	0.78-1.58	1.28	5	0.30-1.44	0.80
	50 to 1,000	71	61*	0.62-4.20	1.60	66†	0.30-3.30	1.19
	Over 1,000	7	7	0.80-2.80	1.64	7	0.56-2.20	1.21
Absent	None	20	20	0.00-0.29	0.04	20	0.00-0.29	0.03

* Twelve patients were not included because only the second-hour test urine was suitable for analysis.
† Five patients were not included because they were unable to void prior to the end of the second hour.

not suitable for azure A determination. Of the remaining 83 cases, 5 secreted less than 50 mg. hydrochloric acid; 71 secreted from 50 to 1000 mg. hydrochloric acid, and 7 secreted in excess of 1000 mg. in one hour (Table 1). Among the same 83 patients, 82 excreted 0.5 mg. or more azure A compound. In 71 patients 0.6 mg. or more of azure A compound was found in the two-hour specimens (Table 2). Only three of

TABLE 2.—*The Results of Azure A Test in Eighty-Three Subjects with Free Gastric HCl*

Test Urine Specimens	Azure A, Mg.	Specimens, No.	Specimens Examined, No.	Specimens Not Examined, No.
1st hour	0.3 or over	39	71	12*
	Under 0.3	32		
2d hour	0.5 or over	74	78	5†
	Under 0.5	4		
2 hr. test	0.6 or over	71‡	71	12*
	Under 0.6	0		

* Only the second-hour test urine was suitable for analysis.
† Five patients were unable to void prior to the end of the second hour.
‡ One patient excreted 1.16 mg. on the repeat examination but only 0.33 mg. on the first test.

these excreted less than 0.5 mg. of the dye during the second hour. In 12 additional cases, only the second-hour specimen was available for analysis, and in 11 of these the azure A compound measured 0.5 mg. or more. In the 12th patient, it was 0.3 mg.; reexamination was not possible, and this incompletely studied case was the only false negative result in the series.

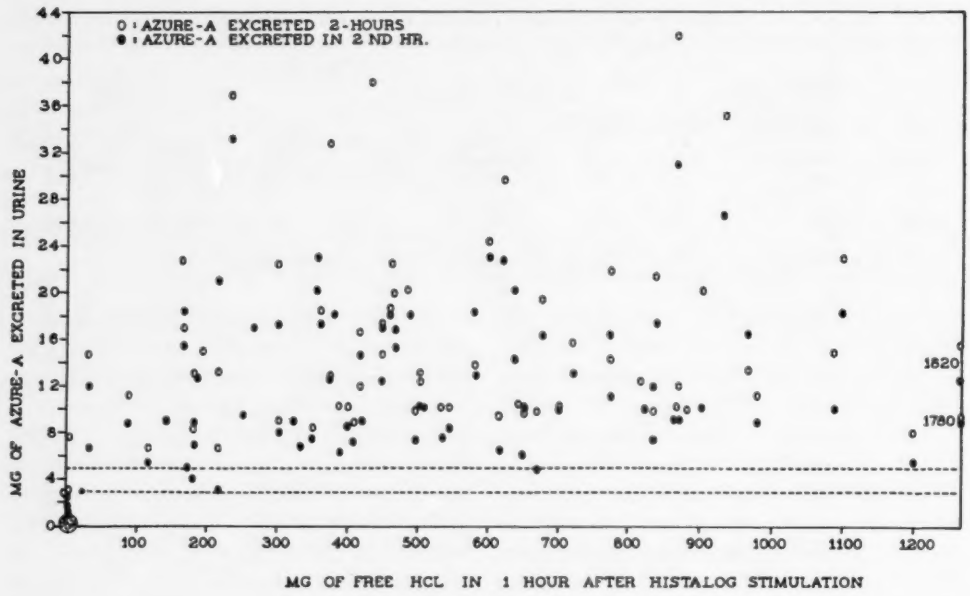
One additional patient with free HCl excreted a red pigment in the urine, preventing the measurement of the azure A compound. The nature of the pigment is not known; this phenomenon has been noted by others.[5]

One patient with an active duodenal ulcer, who secreted 973 mg. HCl in one hour after Histalog stimulation, excreted only 0.33 mg. of azure A compound in the two-hour total test specimen. However, during a second examination 1.16 mg. of azure A compound was recovered in the two-hour test urine.

The milligrams of hydrochloric acid secreted in one hour after the injection of Histalog were compared on a scattergram (Fig.) with the milligrams of azure A compound recovered in the second hour and in the two-hour total test urines. There was no relationship nor any tendency for correlation between the two sets of data, indicating that the azure A ion-exchange compound cannot be utilized to quantitate gastric secretory activity.

The 20 achlorhydric persons included 9 with proved pernicious anemia and one with a total gastrectomy. This group excreted almost no dye during the first hour. Sixteen of the twenty excreted no azure A during the second hour. In the remaining four cases the outputs varied from 0.1 to 0.29 mg. in the two-hour total test specimen. One patient with achlorhydria, after the usual dose of Histalog, excreted 0.30 mg. azure A compound in the second hour and 0.44 mg. in the two-hour total urines. The examination was repeated with a double dose of Histalog; the achlorhydria persisted; the collection of urine at this time was supervised more carefully and contained only 0.1 mg. of azure A compound in the two-hour total test specimen.

During the early phase of the study there were 12 instances in which only the second-hour urine was suitable for the determination of azure A compound. The first hour speci-


O : AZURE-A EXCRETED 2-HOURS
● : AZURE-A EXCRETED IN 2 ND HR.
MG OF AZURE-A EXCRETED IN URINE
MG OF FREE HCL IN 1 HOUR AFTER HISTALOG STIMULATION
1820
1780

Scattergram

men was cloudy in 11 of this group, and its addition to an aliquot of the second-hour specimen also made the two-hour total specimen gray and cloudy. Later, as the information became available,§ such cloudy-gray first hour specimens were reexamined after the addition of a few crystals of aluminum chloride to a 10 cc. aliquot. On one occasion, the addition of the pale yellow first-hour urine to the blue second-hour specimen resulted in a liquid which was almost colorless, grayish, and clear after it was placed in the boiling water bath. The blue color returned to some extent after it stood for 24 hours.

Of the 71 acid-secreting cases in which the first-hour test specimens were suitable for examination, 39 excreted in excess of 0.3 mg. of azure A compound. The results thus indicate that 0.3 mg. or more of azure A compound in the first-hour test urine reflects the secretion of hydrochloric acid (Table 3). More than half of those persons secreting acid will be detected by the examination of only the first-hour test urine. An output of 0.5 mg. or more of the dye in the second-hour specimen also signifies a test positive for hydrochloric acid. The examination of the two-hour total test of urine will be necessary only in a few instances to prove the presence of free hydrochloric acid; it should be performed in all patients with achlorhydria in whom the first hour specimen contains any azure A compound.

§ Segal, H. L.: Personal communication to the authors.

TABLE 3.—*Interpretation of Test*

Free Gastric HCl	Azure A, Mg.		
	In 2 Hr. Total Test Urine	In 2d Hr. Test Urine	In 1st Hr. Test Urine
Present	0.6 or greater	0.5 or greater	0.3 or greater
Absent	0.3 or less	0.3 or less	.....
Borderline	0.3 to 0.6	0.3 to 0.5	.....

COMMENT

Determination of the presence or absence of hydrochloric acid in the gastric contents of patients with gastric lesions obviously is of considerable diagnostic importance. Nevertheless, the procedure is not performed in many patients. There are at least several reasons for this omission; insufficient understanding of the method and the useful information it may provide, the patient's reluctance to swallow a tube, or the lack of trained assistants for this purpose. Tube-

less gastric analysis avoids the problem of swallowing a tube and thereby eliminates the possible effects of the associated tension upon the gastric secretory mechanism. The determination of azure A compound in the urine is simple and does not require trained personnel.

In this series the measurement of azure A ion-exchange compound in the urine after oral administration adequately differentiated the 82 patients with hydrochloric acid from the 20 with achlorhydria. Thus, the presence or absence of anacidity was established in 102 patients by this procedure. These results confirm the observations of Segal and his colleagues. Among the 102 patients, one falsely high and one falsely low case of azure A compound excretion were encountered, both in the borderline group (Table 3). On repeat examination both cases were identified in their proper categories. There was also a single false negative result; this patient was not available for reexamination; moreover, in this case only the second-hour test specimen was suitable for analysis. In another instance in which hydrochloric acid was present, a red pigment interfered with the determination of the blue dye in the urine.

In the absence of maximal stimulation, basal gastric secretion may vary considerably from day to day in the same person. To avoid, in so far as possible, the problem of fluctuating patterns of acid secretion, azure A compound was given immediately following the completion of the usual gastric analysis, taking full advantage of the secretory stimulant Histalog. Nevertheless, there was no quantitative correlation between the ouput of acid in the gastric content and the amount of azure A compound in the urine. It would appear that the excretion of azure A, as with the quinine exchange resin, is influenced by factors other than the rate of gastric secretion.

The azure A ion-exchange compound behaves like the quinine indicator resin. Both are composed of a highly purified carboxylic acid cation exchange resin (Amberlite XE-96). Only the special indicator cation differs, being azure A dye in one and quinine in the other. The ease with which the azure A dye can be identified makes this newer compound a very useful and simple indicator of hydrochloric acid in the gastric content. However, in accord with the findings of Segal and co-workers,[5] the azure A compound cannot be used to estimate acid levels quantitatively. The observation that half of the acid secretors can be detected by the simple inspection of the dilute first-hour test urine is a further simplification of this easily performed test (Table 3).

Impairment of renal function, reduced intestinal absorption, pyloric obstruction, or severe hepatic disease were not present in the current series; these disorders, on theoretical grounds, may interfere with the excretion of azure A and with the accuracy of the procedure.

SUMMARY

Hourly gastric secretion in response to the potent stimulant Histalog and reflected by the urinary excretion of azure A given orally, was compared in 104 patients. Eighty-two of the eighty-four patients with free hydrochloric acid were identified correctly by this method. A red pigment in the urine interfered with the determination in one patient; one test was incomplete and the patient was not available for reexamination; this case was the only false negative. The 20 patients with achlorhydria were identified correctly. One repeat examination was necessary in both the acid-secreting and achlorhydric groups because of the azure A content of the test urine initially fell in the borderline category. There was no quantitative correlation between the urinary azure A content and the amount of hydrochloric acid in the gastric content, as determined by comparing the milligrams of hydrochloric acid secreted in one hour and the milligrams of azure A excreted in the urine during the two-hour or second-hour test periods.

CONCLUSIONS

Tubeless gastric analysis with Azure A compound administered orally, after ade-

quate gastric secretory stimulation, reliably differentiates patients with achlorhydria from those secreting hydrochloric acid.

Tubeless gastric analysis with azure A is not suitable for the quantitative measurement of hydrochloric acid secretion.

The procedure is simple and therefore adaptable for office use and mass screening surveys.

Dr. Walter L. Palmer made available some of the patients in this study.

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Hemopericardium Following Acute Myocardial Infarction

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Hemopericardium occurring in the course of acute myocardial infarction is most frequently due to rupture of the myocardium but may be caused by bleeding from granulation tissue in areas of fibrinous pericarditis.[1] The use of anticoagulants has been associated with an increase in hemopericardium of both types.[2]

Cardiac rupture is probably always fatal, and the more benign type of bleeding is presumably involved when recovery occurs. When anticoagulant therapy is a factor the signs of pericardial fluid may regress soon after the coagulation mechanism is restored to normal. There are detailed reports * of at least three cases of myocardial infarction in which pericardial tamponade occurred and was relieved by the removal of bloody fluid.

This is a report of three cases in which the diagnosis was made clinically and the outcome was favorable.

CASE 1.—On Aug. 10, 1953, a 69-year-old man was hospitalized because of substernal pain of two days' duration. Myocardial infarction was diagnosed, and treatment was given for severe hypotension and pulmonary congestion, with a good response. Bishydroxycoumarin (Dicumarol) was administered.

On Aug. 14 the patient was transferred to the Long Beach Veterans Administration Hospital. On examination he was found to be a well-developed well-nourished white man, in no distress. There were no signs of congestive failure and no apparent cardiac abnormalities. The blood pressure was 100/64; the pulse rate, 100, and the temperature, normal.

The hematocrit value was 45%; the hemoglobin, 14 gm. per 100 cc., and the white blood cell count 7300. The prothrombin activity was 70% of normal. Electrocardiograms (Fig. 1) showed an acute anterolateral infarction.

Bishydroxycoumarin was given in ordinary doses from Aug. 14 to 27, and the prothrombin activity ranged from 10% to 44% of normal, except on Aug. 22, when it was less than 10% (42 seconds). The course was uneventful until Aug. 20, when there was general malaise and anorexia.

On Aug. 26 there were dyspnea, pallor, and distention of the neck veins. The heart was enlarged 2 cm. beyond the left nipple line. The blood pressure was 96/60; the pulse rate, 120, and the temperature, 99 F. The heart sounds were distant, and there were basal rales. There was no pericardial friction rub. Digitalis was given, with no relief. The white cell count was 14,500.

The next day dyspnea and lethargy were marked. The blood pressure was 92/78, and there was a paradoxical pulse. Dullness at the left base was interpreted as Ewart's sign. The left border of the heart extended to the anterior axillary line. The hematocrit value was 30%. The venous pressure was 212 mm. of water, and the circulation time determined with dehydrocholic acid N. F. (Decholin) was 40 seconds.

An x-ray showed cardiomegaly of no specific type. Bishydroxycoumarin was discontinued, and vitamin K was given. The prothrombin level was 19%.

A pericardial paracentesis by the paraxiphoid approach was attempted, and 15 cc. of fluid was withdrawn. This appeared to be pure blood, and it was believed that the right atrium had been entered. The procedure was therefore discontinued, although it seemed to have given some improvement.

On Aug. 28 the situation was still critical. Upright and supine chest x-rays (Fig. 2) showed widening of the superior mediastinum in the latter, confirming the impression of pericardial fluid. The prothrombin level was 29%.

Pericardial paracentesis was performed, and 350 cc. of bloody fluid was removed. During the pro-

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From the Medical Service of the Veterans Administration Hospital.

* References 3-5.

cedure all the signs of pericardial tamponade diminished. The hematocrit value of the fluid withdrawn was 20%, and that of venous blood taken at the same time was 32%.

The next day the venous distention was gone; the lungs were clear; the pulse was 90, and the patient felt much better. The blood pressure was 110/85. By Aug. 31 the prothrombin time was normal. A pericardial friction rub was heard between Sept. 3 and 10. On Sept. 11 the hematocrit value was 40%.

An x-ray on Sept. 22 (Fig. 2) showed a marked decrease in heart size, and there was only slight

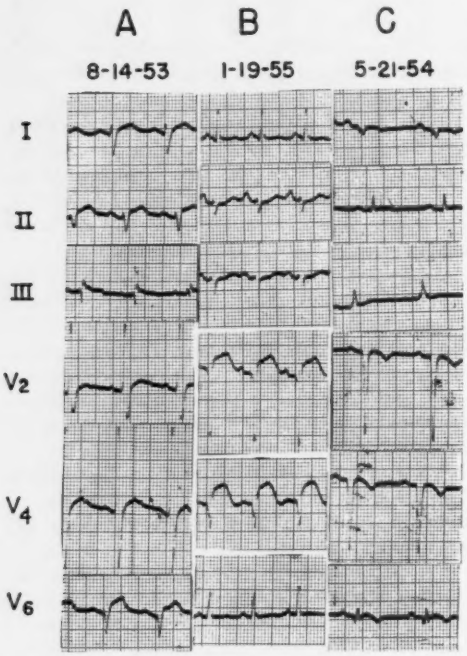

Fig. 1.—Electrocardiographic tracings of Cases 1 (*A*), 2 (*B*), and 3 (*C*), showing acute myocardial infarctions.

left ventricular enlargement. After relief of the pericardial tamponade convalescence was completely satisfactory. When seen eight months later the patient had no complaint of chest pain and there were no signs of congestive failure.

CASE 2.—On Jan. 18, 1955, a 50-year-old man was admitted to the Long Beach Veterans Administration Hospital because of intermittent substernal pain of three days' duration.

On examination he was restless with pain but there were no signs of congestive failure and the heart appeared normal except for occasional premature contractions. The blood pressure was 160/120; the pulse rate, 120, and the temperature, normal.

The hematocrit value was 48%, and the white blood cell count, 11,200. An electrocardiogram (Fig. 1) showed acute anterior myocardial infarction. From Jan. 19 to 21 a gallop rhythm was present. Heparin, 100 mg., was given intramuscularly every eight hours in addition to usual doses of bishydroxycoumarin.

On Jan. 22 there was substernal pain which was aggravated by respiration. The skin was pale and sweaty, and the neck veins were abnormally distended. The heart was enlarged 2 cm. beyond the midclavicular line. There was a loud pericardial friction rub, and the heart sounds were less intense than before. There was a paradoxical pulse. There was no dyspnea, and the lungs were clear. The liver became enlarged and tender. Near the left base there was an area of dulness, bronchial breathing, and egophony. The blood pressure was 95/80; the pulse rate, 126, and the temperature, 100 F.

Preparations were made to do a pericardial paracentesis if the situation should become worse. Anticoagulants were discontinued. Digitalis was given. The prothrombin activity was 32%.

During the next two days the color improved and the blood pressure was 100/70, with a pulse rate of 110. On Jan. 24 the prothrombin time was 64 seconds (activity less than 10% of normal). Vitamin K was given. An x-ray showed nonspecific cardiomegaly. The hematocrit value was 36%, and the white blood cell count, 7000.

The heart size gradually decreased to normal, and the signs of congestion disappeared. Digitalis was discontinued. The prothrombin time returned to normal.

On Jan. 30 there was a sudden onset of numbness and absence of pulses in the left leg. The heart and lungs appeared normal except for a crunching pericardial friction rub which had been present continuously since its first appearance.

A laparotomy was performed under spinal anesthesia, and an embolus was removed from the left common iliac artery at its bifurcation. Postoperatively all the normal pulses were palpable. Beginning 12 hours after surgery, 100 mg. of heparin was given intramuscularly every eight hours.

For several days the course was satisfactory. The friction rub was not heard, and the only abnormalities referable to the heart were a mild tachycardia and a localized area of egophony medial to the tip of the left scapula.

On Feb. 13 there was again a complaint of substernal pain, which was worse with respiration. There was a minimal increase in venous pressure. The lungs were clear except for Ewart's sign. The heart was enlarged 2 cm. beyond the midclavicular

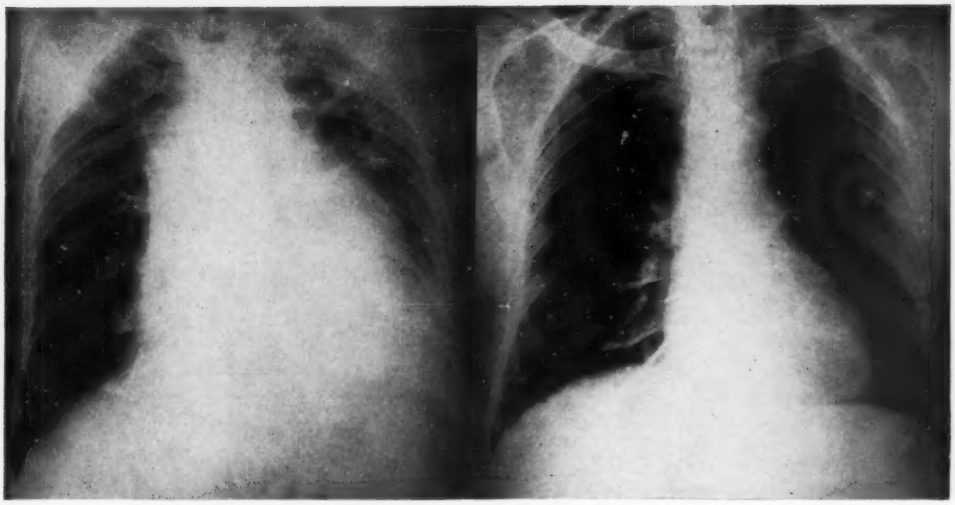

Fig. 2.—Comparable upright chest x-rays in Case 1 at the time of pericardial tamponade (Aug. 28, 1953) and following maximum improvement (Sept. 22, 1953).

line, and there was a paradoxical pulse. The liver was enlarged. There was a harsh pericardial friction rub. The blood pressure was 98/74; the pulse rate, 120, and the temperature, 102 F. The circulation time was 26 seconds with dehydrocholic acid. The white blood cell count was 15,500, and the hematocrit value, 42%.

A presumptive diagnosis of recurrent pericarditis with hemopericardium was made, and heparin was discontinued. Coagulation time (Lee-White) eight hours after the last dose of heparin was normal.

Four days later the blood pressure was 100/65; the pulse rate, 90, and the other findings were unchanged. The friction rub persisted until Feb. 19.

An x-ray on Feb. 24 showed cardiac enlargement, chiefly left ventricular. The lungs were mildly congested, and there was a moderate left pleural effusion. A thoracentesis was performed, and 300 cc. of amber fluid was aspirated at the left base. This fluid contained 1120 white blood cells per cubic millimeter and no red blood cells, and the specific gravity was 1.020.

The signs of congestion gradually abated, and convalescence progressed slowly, being further complicated by an episode of paroxysmal auricular fibrillation and the presence of a pulsus alternans after light activity. The heart remained slightly enlarged. The patient was ambulatory and without symptoms on discharge, April 4.

Case 3.—On May 5, 1954, a 38-year-old man was hospitalized because of chest pain which had begun the day before. An acute myocardial infarction was diagnosed, and bishydroxycoumarin was given so that from May 7 to 19 the prothrombin activity was between 10% and 34% of normal (49 to 21 seconds). The hematocrit value was 46%, and the hemoglobin, 13.9 gm. per 100 cc.

On May 6 and from May 10 to 18 a pericardial friction rub was heard. Because of cough, fever, and signs at the left base, penicillin was given.

On May 20 the patient was transferred to the Long Beach Veterans Administration Hospital. On examination the heart was found to be enlarged to the left and there was a loud pericardial friction rub. There were a few basal rales, and near the left base there was an area of bronchophony and increased tactile fremitus. There were no peripheral signs of congestion.

The blood pressure was 90/50; the pulse rate, 84, and the temperature, 99.4 F. The hematocrit value was 37%, and the hemoglobin, 11.6 gm. per 100 cc. The prothrombin activity was 46% of normal on May 22 and normal thereafter. An electrocardiogram (Fig. 1) showed an acute anterior infarction.

On May 21 a chest x-ray (Fig. 3) showed marked cardiac enlargement suggestive of pericardial fluid. No further anticoagulants were given. Digitalis was administered.

Between May 21 and June 1 there was a weight loss of 12 lb. and the temperature dropped to normal. With this there was subjective improvement. On June 1 the cardiac enlargement and consolidation at the left base were less, and on June 7 an x-ray (Fig. 3) showed a remarkable decrease in heart size. The blood pressure stabilized at 120/75. On June 8 the hematocrit value was 45%. The patient was discharged on June 15 in good condition.

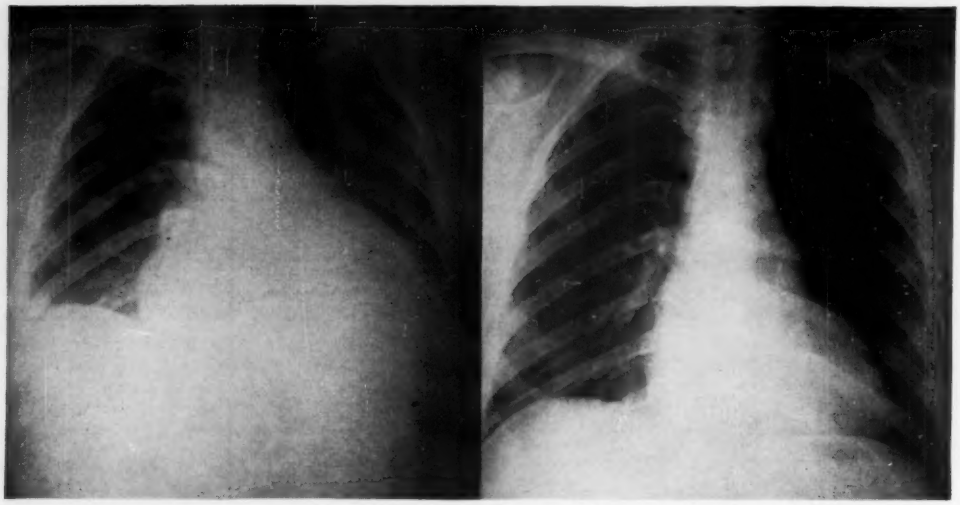

Fig. 3.—Chest x-rays in Case 3 at the time of diagnosis of hemopericardium (May 21, 1954) and after improvement (June 7, 1954).

COMMENT

Pericardial tamponade is a phenomenon not ordinarily expected in myocardial infarction. The signs may be almost indistinguishable from those of myocardial failure, which is commoner.

A prolonged pericardial friction rub is usually heard in cases of hemopericardium and should suggest this diagnosis as a complication of infarction. Previous reports emphasize the importance of anticoagulant therapy as a predisposing factor, and the present series illustrates this relationship.

In the first case reported, as in the one of Rose and co-workers,[3] removal of a large amount of pericardial blood completely relieved the circulatory failure. In the second there was a combination of tamponade and failure. Widespread electrocardiographic changes and a gallop rhythm were observed early in the course of the illness and suggested a severe degree of myocardial damage, but the sudden deterioration four days after admission, with a narrow pulse pressure, distended veins, friction rub, and anemia, must have been due to pericardial bleeding. The gallop rhythm was not heard at that time, and there were no pulmonary rales. A few days later the heart size was again normal by percussion. A later episode was similar except that the heart remained large and x-rays then showed the configuration of left ventricular enlargement. Therefore, it is thought that tamponade and failure were both present, with each predominating at different times.

The same situation was present in the cases of Syner [4] and Anderson and co-workers.[5] In these there was relief of tamponade by removal of small amounts of fluid (125 and 75 cc., respectively) but there was residual evidence of myocardial insufficiency. In one case an enlarged heart was found at autopsy, and in the other it was necessary to treat the patient actively with digitalis, diuretics, and a low-sodium diet after treatment of the tamponade.

The summation of the effects of pericardial disease and myocardial failure was shown in a case of calcified pericardium studied by cardiac catheterization by Harvey and co-workers.[6] The hemodynamics were characteristic of constrictive pericarditis when the heart was enlarged. After medical treatment for congestive failure the heart became smaller, and the same studies then showed no significant constriction.

In the third case reported here, Ewart's sign was misinterpreted and led to a diag-

nosis of pneumonia. It was not until an x-ray was taken that pericardial fluid was recognized. There was improvement soon after the prothrombin time returned to normal.

SUMMARY AND CONCLUSIONS

Three cases of hemopericardium complicating acute myocardial infarction are presented.

It is postulated that the greater the tendency toward left ventricular failure and dilatation the less will be the amount of fluid which will produce tamponade and the more difficult it is to make a diagnosis of tamponade.

It is important to detect pericardial bleeding and to distinguish it from myocardial failure. Pericardial paracentesis may be necessary.

In the second case, a successful common iliac artery embolectomy was done 15 days after the onset of the pain of severe myocardial infarction.

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Myocardial Infarction with Special Reference to the Negro

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and
LIEUT. COL. PHILIP G. KEIL (MC), U. S. A. F.

From the standpoint of morbidity and mortality, coronary atherosclerosis is the paramount medical problem in the United States. This condition is the most commonly fatal type of heart disease and is the greatest single cause of death from disease in this country.[1] The Editor of *The Journal of the American Medical Association* recently pointed out that more than one in five physicians' deaths is caused by this condition, more than twice as many as from cancer.* Not only has the incidence of coronary artery disease increased with the ever-expanding proportion of elderly persons in the population but it has also become the major cause of disability and death among persons in their most economically productive years of life.[4]

Until the pathogenesis of coronary atherosclerosis is better understood, no effective prevention or treatment is possible. Despite intensive investigation, its etiology remains obscure. It occurred to us that basic information concerning the natural history of this disease might be obtained by studying its manifestations in young persons. Therefore, 34 cases of proved myocardial infarction observed at the Maxwell Air Force Base Hospital during a four-year period were carefully reviewed.[5] Of significance was the observation that not one of these patients was a Negro, in spite of the fact that 15% of admissions to the hospital were Negroes. Because of this finding, the literature was reviewed, and a decided difference of opinion as to the incidence of coronary occlusion in Negroes was discovered. White[6] states in his latest book that race appears to have but slight bearing on the occurrence of coronary heart disease. He adds that at one time it was thought that coronary atherosclerosis was uncommon in the Negro but that this view has now been invalidated. Others, however, report this disease to be less frequent in the Negro race.[7]

We therefore decided to compare salient features of coronary artery disease in white and Negro patients.

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From the Medical Service, United States Air Force Hospital, Maxwell Air Force Base, Alabama.

* References 2 and 3.

OBSERVATIONS

The clinical records of 330 patients with myocardial infarction were reviewed. In each instance the diagnosis was established by necropsy findings or by definite electrocardiographic changes in association with the clinical picture. The records were those of a large midsouthern university hospital where the ratio of admissions was approximately 70% Negro and 30% white. Male and female admissions within each race were essentially equal.

Incidence.—There were 162 white patients with myocardial infarction, as compared with

Incidence of 330 Myocardial Infarctions by Decades

Decade	White Men	White Women	Negro Men	Negro Women
3rd	0	0	0	1
4th	4	0	3	6
5th	12	3	13	25
6th	26	9	18	21
7th	36	10	26	17
8th	37	16	19	12
9th	7	2	3	2
10th	0	0	2	0
Total	122	40	84	84

168 Negroes. Only 40 of the 162 in the white race were women, while 122 were men. In the Negro, the incidence was equal, with 84 patients of each sex.

Age Groups.—The age of occurrence of the initial myocardial infarction by decades, sex, and race is shown in the accompanying Table. Of special interest is the fact that 38% of Negro women (32 of 84) had suffered a myocardial infarct prior to reaching the age of 50, or before the sixth decade of life. Only 7.5% (3 of 40) white women had an infarct prior to 50, while 13% (16 of 122) of white men and 19% (16 of 84) of Negro men had experienced an infarction before the beginning of the 50th year (Fig. 1).

Of further interest is the fact that the great difference in the age of occurrence between the Negro and white women persisted at least to the age of 60, or to the start of the seventh decade. Sixty-three per cent (53 of 84) of the Negro women had infarcts prior to 60 years of age, as contrasted with only 30% (12 of 40) of white women (Fig. 2). This is a ratio of more than 2:1.

Family History.—White Men: Thirty-seven (30%) had a positive family history; twenty (16%) had no family history of cardiovascular disease, and in sixty-four (54%) there was no adequate record.

White Women: Sixteen (40%) had a positive family history; eight (20%) had no family history, and in six (40%) this was not recorded.

Negro Men: Eighteen (21%) had a positive family history; twelve (14%) had no family history, and in fifty-four (65%) it was unknown.

Negro Women: Twenty-seven (32%) had a positive family history; sixteen (19%) had a negative family history, and in forty-one (49%) it was unknown.

Obesity.—White Men: Thirty-five (29%) were obese; sixty-three (52%) were of average weight; sixteen (13%) were underweight, and in eight (6%) there was no record of the weight.

White Women: Twenty-five (62.5%) were overweight; twelve (30%) were of average weight, and in three (7.5%) the weight was unknown.

Negro Men: Twenty-six (31%) were obese; thirty-seven (44%) were of average weight; eleven (13%) were underweight, and in ten (12%) there was no information about body build.

Negro Women: Fifty-five (65%) were overweight; nineteen (23%) were of average weight; only three (4%) were underweight, and in seven (8%) the weight was unknown.

Blood Pressure.—White Men: Fifty-six (46%) had a history of hypertension; fifty-eight (48%) were normotensive, and in eight the blood pressure was unknown.

White Women: Twenty-four (60%) had a history of hypertension; sixteen (40%) were normotensive.

Negro Men: Forty-three (51%) had a past record of hypertension; thirty-two (38%) were normotensive, and in nine this history was unobtainable.

Negro Women: Fifty-four (64%) had hypertension; twenty-four (29%) were normotensive, and in six the blood pressures were unknown.

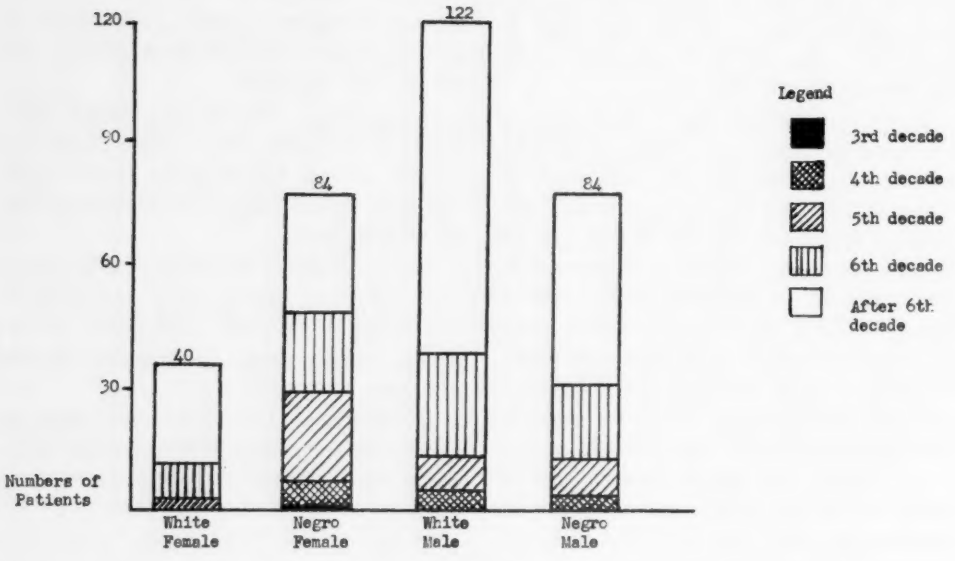
Angina.—White Men: Fifty-six (46%) had a history of angina; fifty-two (43%) did not, and in fourteen there was no adequate record.

White Women: Twenty-four (60%) had experienced angina; nine (22.5%) had no history of this symptom, and in seven there was no adequate record.

Negro Men: Twenty-six (31%) had a history of angina; forty-one (45%) had no such history, and in seventeen there was no adequate clinical summary.

Negro Women: Twenty-one (25%) had a history of angina; fifty (59%) did not, and in twelve this feature was not recorded.

Multiple Infarctions.—White Men: Sixteen (13%) of the one hundred twenty-two white man had multiple infarctions, including one patient under 40 years of age.



330 MYOCARDIAL INFARCTIONS

Occurrence by color, race and decade to age 60

Figure 1

124 MYOCARDIAL INFARCTIONS IN FEMALES

Sex and Age at Occurrence by Decades

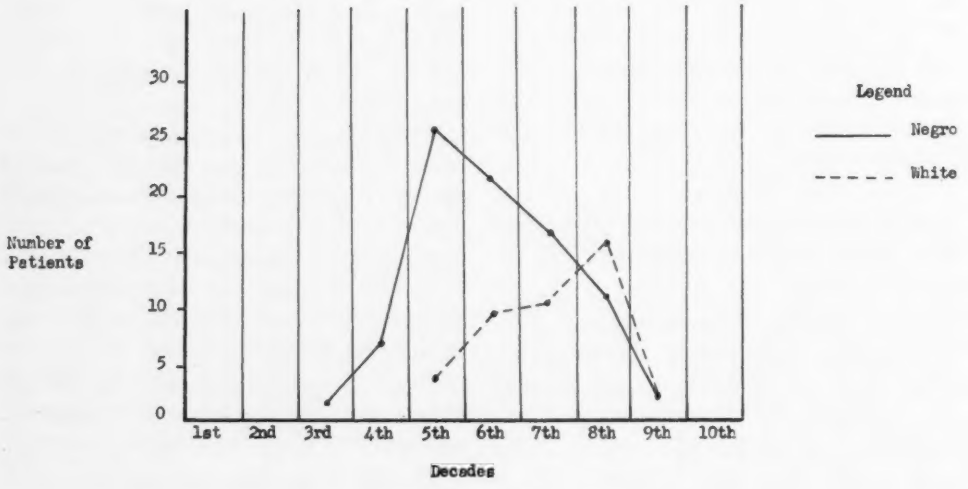


Figure 2

White Women: Two (5%) of the forty white women experienced multiple infarctions. Neither person was under the age of 40.

Negro Men: Five (6%) of the Negro men had multiple infarctions. None of these five was under the age of 40.

Negro Women: Six (7%) of the Negro women had multiple infarctions; not one of these was under the age of 40.

Multiple repeated infarcts did not explain the high mortality rate. Most of the persons in this series died with or as a direct result of the first myocardial infarction.

Associated Disease.—There was no unusual incidence of associated disease among the white men. Among the white women seven (17.5%) had diabetes, three had complicating malignant disease, and one had gall-bladder disease. Twelve of the Negro women had diabetes (14%), and one had a malignant disease. Two of the Negro women who experienced myocardial infarction under the age of 40 gave the history of previous toxemia of pregnancy.

Incidence of Death.—Seventy-eight (64%) of one hundred twenty-two white men diled as a result of their disease. Of interest was the death of three (75%) of four white men who suffered myocardial infarctions before the age of 40 years.

Thirty-two (80%) of forty white women died of the disease. None was below the age of 40.

Fifty-six (66%) of eighty-four Negro men died of the disease; one was under 40 years of age.

Sixty-eight (81%) of eighty-four Negro women died of the disease; three were under 40 years of age.

COMMENT

The etiology of coronary atherosclerosis remains one of the most important unsolved problems in medicine. In spite of a vast amount of research, the cause of this disease is uncertain. Therefore, its prevention and treatment are unsatisfactory. Investigations to determine its etiology have been primarily influenced by the strikingly greater frequency of this disease in men. The incidence in males, as compared with females, has been variously reported as ranging from 2:1 to more than 6:1.† The most interesting and highly significant ratio has been reported in two separate groups of 100 patients, each under the age of 40 years, having coronary heart disease with or without myocardial infarction.‡ In the first group [10] there were 96 males and 4 females (a ratio of 24:1), while in the second [6] there were 97 males and 3 females (a ratio of 32:1). According to White, "These findings must be of great significance in any consideration of the etiology of coronary heart disease." It would certainly seem that some factor must be operating which is peculiarly lethal to males. Dock [11] has stated that any acceptable concept of the pathogenesis of coronary atherosclerosis must explain this striking sex difference. He has reported a greater thickness of the coronary artery in the male than in the female infant.[11] The significance of this finding has been disputed by others.[12]

The common experience that there is a marked disparity in the average degree of coronary atherosclerosis between men and women of comparable ages has led to the widespread view that an ovarian hormonal factor may be responsible for the protection of women, especially those under the age of menopause.§ In accord with this concept Barr [16] has reported that the administration of estrogen to survivors of myocardial infarction can convert the lipid pattern in the plasma toward that observed in so-called normal persons. Also, Gertler and Garn [17] found a surprisingly low incidence of coronary heart disease in a large group of eunuchs.

In the present study of 330 cases, the incidence of myocardial infarction in Negroes was found to be only 42% of that in white patients. It should be noted that all of these persons were from a similar economic strata

† References 8 and 9.

‡ References 6 and 10.

§ References 13 and 15.

and had comparable dietary habits. The most interesting observation, however, was the absence of any difference in incidence between Negro men and Negro women. Myocardial infarction occurred earlier in the Negro woman than in the Negro man, white man, or white woman. The average age in the Negro woman was 10 years less than that of the white woman, 7.7 years below that of the white man, and 6.7 years under the Negro man. Of 14 patients under the age of 40 who experienced a myocardial infarction, 7, or 50%, were Negro women, 4, or 29%, were white men, while 3, or 21%, were Negro men. There was not a single comparable case among the white women. It is most interesting to note that all seven of these Negro women were reported as continuing to have normal menses. In one instance a left oophorectomy had been performed three years previously. It is obvious that coronary atherosclerosis in the Negro woman must be investigated in a comprehensive manner.

In general, the incidence of familial history of cardiovascular disease was somewhat higher in the women of both races than it was in the men. Also, the majority of the feminine patients were overweight, while the majority of the men were of average weight. In addition, the women had a higher incidence of hypertension than the men. Race seemed to play no part in the incidence of familial cardiovascular disease, obesity, or hypertension. A rather striking difference was noted as regarded the occurrence of angina. Only 25% of Negro women and 31% of Negro men reported a history of angina pectoris, while 50% of white men and 60% of white women had a definite history of this symptom. There were relatively few multiple infarctions in this series, the highest percentage (13%) occurring in the white man. There was no unusual incidence of associated disease other than the observation that diabetes was much commoner in the women than in the men, 17.5% in the white women and 14% in the comparable Negro sex.

The remarkable findings in the Negro women observed in the present investigation cast considerable doubt upon many established concepts of coronary artery disease. Further analysis of these results is essential. It would appear that the present study provides a stimulating approach to the investigation of the pathogenesis of coronary atherosclerosis.

SUMMARY AND CONCLUSIONS

In the present series of 330 cases of proved myocardial infarction, the incidence in Negro patients was 42% of that in white patients.

Myocardial infarction was equally frequent among Negro men and women, while among the white patients it was three times as common among the men.

The average age at the time of myocardial infarction in the Negro woman was 55 years, as compared with 65 years for the white woman, 61.7 years for the Negro man, and 62.7 years for the white man.

Obesity, diabetes, hypertension, and a family history of cardiovascular disease occurred with approximately equal frequency in the Negro and white patients. However, while 60% of white women had a definite history of angina, this was true in only 25% of Negro women.

Further investigation of coronary atherosclerosis and myocardial infarction in the Negro woman is essential.

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Allergic Reactions to Paraaminosalicylic Acid

Report of Six Cases

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P-Aminosalicylic acid (PAS) has become the standard adjuvant drug for use with streptomycin or isoniazid in the treatment of tuberculosis. Courses of streptomycin and PAS or isoniazid and PAS are now usually given throughout a patient's sanatorium residence, and many patients are discharged from sanatoriums to continue chemotherapy at home. Other tuberculous patients get drug treatment at home without ever entering a sanatorium. Such home chemotherapy continues for months and occasionally, in cases with inoperable cavities, for years. Sensitization reactions to PAS occur in about 4% of cases.[1] Streptomycin reactions are less common, and those to isoniazid, very rare. PAS reactions assume many forms, and their management in a patient who needs chemotherapy for active or recently active tuberculosis can present serious problems. These problems confront not only chest specialists but also internists, surgeons, and general practitioners, who are more and more frequently called upon to supervise home chemotherapy in tuberculous patients.

Toxic reactions to PAS are confined largely to the gastrointestinal tract, with the familiar diarrhea, nausea, vomiting, and abdominal distress apparently resulting from local irritation.

Of the allergic reactions to PAS, drug fever and skin eruptions are most commonly encountered. Others previously described and cited by Warring and Howlett [1] in their important paper on the subject are as follows: headache; a syndrome characterized by burning of the eyes, lacrimation, and conjunctival irritation; transient lymphadenopathy; angioneurotic edema; symptoms suggesting anaphylactic shock; spasmodic cough and wheezing; hepatitis *; granulopenia; reactions resembling infectious mononucleosis; a syndrome simulating meningitis.[4]

Warring and Howlett [1] described seven patients of their own with sensitivity reactions to PAS, including one with Löffler's syndrome.[5] Desensitization was successful in four of their cases, starting with minute doses of PAS and gradually increasing to full dosage.

Lichtenstein and Cannemeyer [2] reported eight cases of severe PAS hypersensitivity. Several had sudden onset with fever, adenopathy, and atypical lymphocytes suggesting infectious mononucleosis. In the remainder of their cases vomiting, hepatomegaly, splenomegaly, and abnormal liver-function tests indicated hepatitis. All had skin eruptions. Two cases of jaundice in patients taking PAS were reported by Hayes and Weiss.[3] Both patients were later desensitized. The desensitization programs in these cases started with 10 to 50 mg. of PAS, and dosage was gradually increased to standard amounts over a period of approximately 50 days. If reactions occurred during desensitization, they reinstituted dosage at a lower level. Crofton [6] used a more rapid desensitization schedule, starting at 0.5 gm. and reaching full dosage in 10 to 14 days. If a reaction occurred, he recommended resuming desensitization after the re-

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* References 2 and 3.

action had subsided, starting with the dose last used. Test doses of PAS may cause severe reactions in hypersensitive persons. A fatality has been reported [7] which followed a test dose of 5.5 gm. of PAS. Death in this case was apparently due to adrenal insufficiency.

At the Middlesex County Sanatorium we have used *p*-aminosalicylic acid since 1949, and we now follow the current practice of giving 10 or 12 gm. daily to every patient starting a course of daily or twice-weekly streptomycin. We substitute isoniazid as the accompanying drug for patients who cannot tolerate PAS because of severe, repeated gastrointestinal irritation or a serious allergy not amenable to desensitization. The gastrointestinal symptoms occur less often if the total daily dose, divided into four parts, is given after each meal and with a bedtime lunch. The powdered drug dissolved in water is better tolerated than PAS in tablet form, and the sodium *p*-aminosalicylate is less irritating than the acid.

The cases reported below illustrate varied types of hypersensitivity reactions to PAS.

REPORT OF CASES

CASE 1.—(Fig. 1) *Skin eruption*

C. G., a 59-year-old man, had streptomycin 1 gm. twice weekly and PAS 10 gm. daily for four months, starting April, 1951, without reactions. Another course of streptomycin and PAS was administered starting Jan. 15, 1952. On May 10, 1952, he developed pruritic eruption on the calves of the legs, later involving the hands, groin, and lower abdomen. Thirteen days later streptomycin and PAS were discontinued (Fig. 1) and he was given isoniazid 300 mg. daily alone. The skin lesions gradually improved and had entirely disappeared by Sept. 1, 1952. On Sept. 19 PAS was added in the usual dosage. Two days after PAS was resumed the eruption reappeared on the lower extremities and isoniazid and PAS were discontinued. When the rash had again disappeared, PAS was resumed, starting with 0.01 gm. daily and increasing the dosage by small increments until the patient was again on full dosage three weeks later. The eruption did not recur, and isoniazid 300 mg. daily was added. On May 15, 1953, because of progression of disease, strepomycin, 1 gm. twice weekly, was added

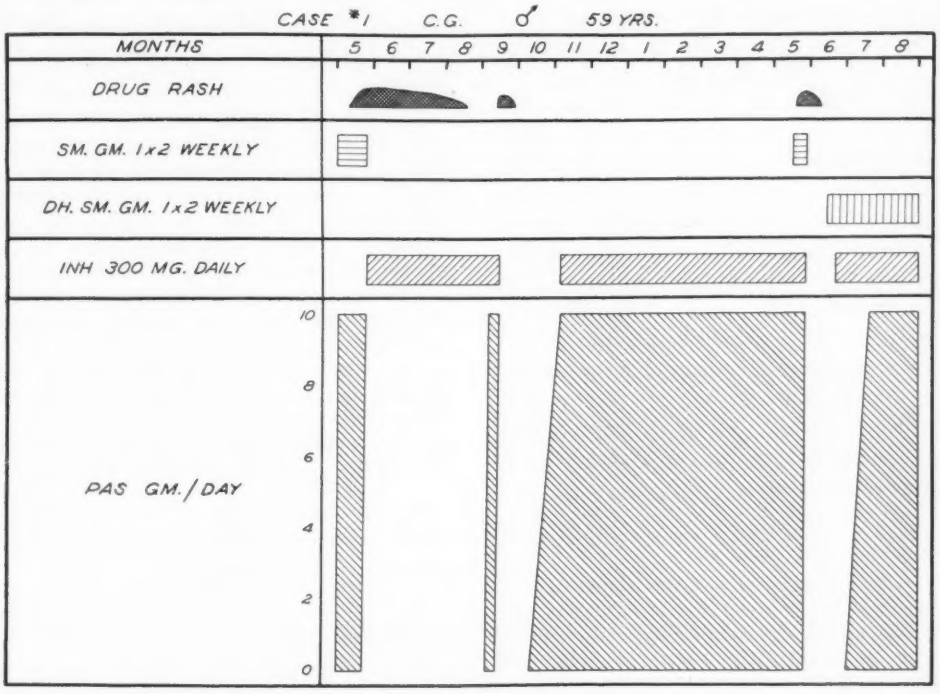


FIG. 1

to the isoniazid and PAS. A macular rash reappeared on the legs, thighs, and groin, and PAS, isoniazid, and streptomycin were discontinued. The rash again subsided. Chemotherapy was resumed, starting with dihydrostreptomycin alone. As there was no recurrence of the eruption, isoniazid was added a week later, followed soon after by another desensitizing course of PAS which was increased to full dosage. All three drugs have been continued since, without recurrence of the dermatitis.

Comment.—The recurrence of the rash when PAS was added to isoniazid showed sensitivity to PAS, but after desensitization to PAS there was no further recurrence until streptomycin was added to isoniazid and PAS, when the rash again appeared. Dihydrostreptomycin plus isoniazid had failed to cause recurrence of the rash, and PAS in desensitizing doses was well tolerated. This patient was therefore allergic to PAS and possibly also to streptomycin but was successfully desensitized to PAS, and dihydrostreptomycin substituted for streptomycin was tolerated. His reaction when streptomycin was added may have been a manifestation of sensitivity to this drug or an example of the "nonspecific flare-up" described by Sulzberger,[8] in which lesions first produced by one agent may become exacerbated on exposure to another.

CASE 2.—*Skin eruption, generalized, with mild exfoliation, fever, and chills*

H. R., a 46-year-old man, was admitted Nov. 18, 1953, with moderately advanced pulmonary tuberculosis and tuberculosis of the larynx. Streptomycin 1 gm. daily and PAS 10 mg. daily were started Nov. 21, 1953. On Dec. 18, 1953, he became ill with temperature of 101 F, chills, and sweating. He also developed a morbiliform pruritic eruption covering his trunk and extremities. Both streptomycin and PAS were discontinued. Five grams of PAS was given on Dec. 23 as a test dose, followed again by chills and fever, this time with nausea. No further PAS was given. On Dec. 26, dihydrostreptomycin 1 gm. daily and isoniazid 300 mg. were started and continued for two days, when, immediately following a dihydrostreptomycin injection, there was a reaction with temperature of 99 F and a mild chill. The dihydrostreptomycin and isoniazid were discontinued. On Jan. 9, 1954, there was still a diffuse erythema with mild exfoliation. Sensitivity to PAS had definitely been demonstrated by the reaction to the test dose, and the patient was presumably also sensitive to dihydrostreptomycin, having reacted immediately after an injection of this drug. By Jan. 3, 1954, the skin eruption had disappeared and there was no more itching. Dihydrostreptomycin administration was resumed on that date, starting with 0.01 gm. and increasing gradually over a 10-day period to 1.0 gm. daily. No further reaction occurred. On Feb. 16 isoniazid was added, and both drugs were continued for nine months longer without further reactions.

Comment.—This patient was sensitive to PAS and also, presumably, to dihydrostreptomycin. He was desensitized to dihydrostreptomycin. No attempt was made to desensitize him to PAS because of the severity of the skin eruption, which was mildly exfoliative.

CASE 3.—*Skin eruption limited to the scrotum*

M. M., a 48-year-old man, was started April, 1952, on a course of streptomycin 1 gm. daily, and after six weeks he was given 1 gm. twice weekly with PAS 10 gm. daily. In August, 1952, he developed a pruritic dermatitis confined to the scrotum which did not respond to local antibacterial and fungicidal therapy. When streptomycin and PAS were discontinued, the eruption disappeared within one week. Two weeks later PAS alone was resumed, the dosage starting with 0.01 gm. and gradually increasing until the patient was on full dosage at the end of 18 days. There was no recurrence of the eruption, and streptomycin was resumed with full dosage. The eruption never recurred.

Comment.—This was a localized dermatitis caused by PAS, and the patient was successfully desensitized.

CASE 4.—*Skin eruption, fever, hepatitis, monocytosis, eosinophilia.*

M. L., a 47-year-old housewife, was admitted on Jan. 12, 1954, with slight progression of a minimal lesion in the right upper lung field. Streptomycin 1 gm. twice weekly and PAS 10 gm. daily were started Jan. 20. On Feb. 16 an itching papular rash appeared on her arms, posterior chest, and abdominal wall. Streptomycin and PAS were accordingly discontinued. Two days later she developed joint pains, headache, and small vesicles in the mouth. Her admission differential blood count had shown no eosinophiles, but on Feb. 19, three days after the skin reaction, there was a 7% eosinophilia. The following day, Feb. 20, her temperature rose to 102 F, falling to 98.6 F in the next four days. The pruritic eruption was still present. Jaundice appeared on March 4, with dark urine positive for bile and clay-colored stools. At that time her total white blood cell count was 18,750, with 56% lymphocytes; bilirubin total, 2.2 mg.; direct-reacting,

1.7 mg.; indirect-reacting, 0.5 mg.; cephalin flocculation, 3+ in 24 hours and 48 hours; alkaline phosphatase, 5.4 Bodansky units. Her liver and spleen were not palpable. Another serum bilirubin determination March 10 showed a total of 7.7 mg.; direct-reacting, 6.1 mg.; indirect-reacting, 1.6 mg. Heterophile agglutination tests were negative then and on three subsequent determinations in the succeeding five weeks. The jaundice gradually faded and by April 6 was no longer present, with icterus index down to 6 on April 8. A sulfobromophthalein (Bromsulfalein) test on May 24 showed no retention of dye, although the cephalin-flocculation test was still 3+ and 4+ in 24 and 48 hours and thymol turbidity was 10.1 units per 100 cc. The total white blood cell count was down to 6800 on May 24, with 43% lymphocytes. The lymphocytes since the onset of the jaundice had been of the type seen in infectious mononucleosis. Eosinophilia reached a maximum of 27% on March 12, falling to 0 on May 24. She was discharged May 26, 1954, to continue to rest at home under close observation. Cephalin-flocculation test was 4+ in 48 hours on July 30. Her pulmonary lesion was stable.

Comment.—This case of hepatitis with some of the features of mononucleosis resembles those described by Lichtenstein. In spite of the initial skin rash and arthralgia, the hepatitis which followed could have been on an infectious basis. If it was, however, a hypersensitivity phenomenon, the allergen was presumably PAS. Because of the seriousness of the reaction and the stability of the pulmonary lesion, no test dosages or attempts at desensitization were tried.

CASE 5. (Figure 2).—*Fever, rash, leucopenia, gingivitis, cervical adenitis*

L. C., a 35-year-old woman, was started on a course of streptomycin 1 gm. daily by her local physician on July 25, 1949, sixteen days prior to admission to the sanatorium. On July 31 she developed chills, sweats, and a temperature of 102 F, with a generalized erythematous rash. Streptomycin was discontinued. Dihydrostreptomycin was tried on Aug. 6, and this too was followed by a reaction with temperature of 100.8 F. After admission here Aug. 9, streptomycin was tried again, tripelennamine (Pyribenzamine) hydrochloride 100 mg. being given at 12 noon and 4 p. m. on the day of injection, but in spite of the antihistamine nausea, vertigo, and temperature of 100 F developed within two and one-half hours of the streptomycin injection. On March 22, 1950, a course of PAS alone,

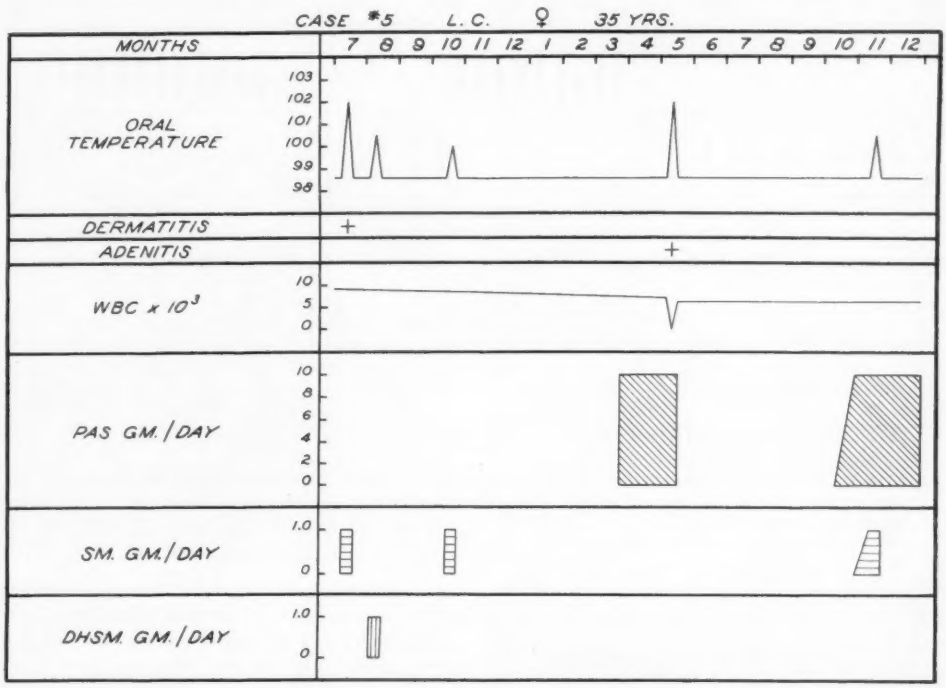


FIG. 2

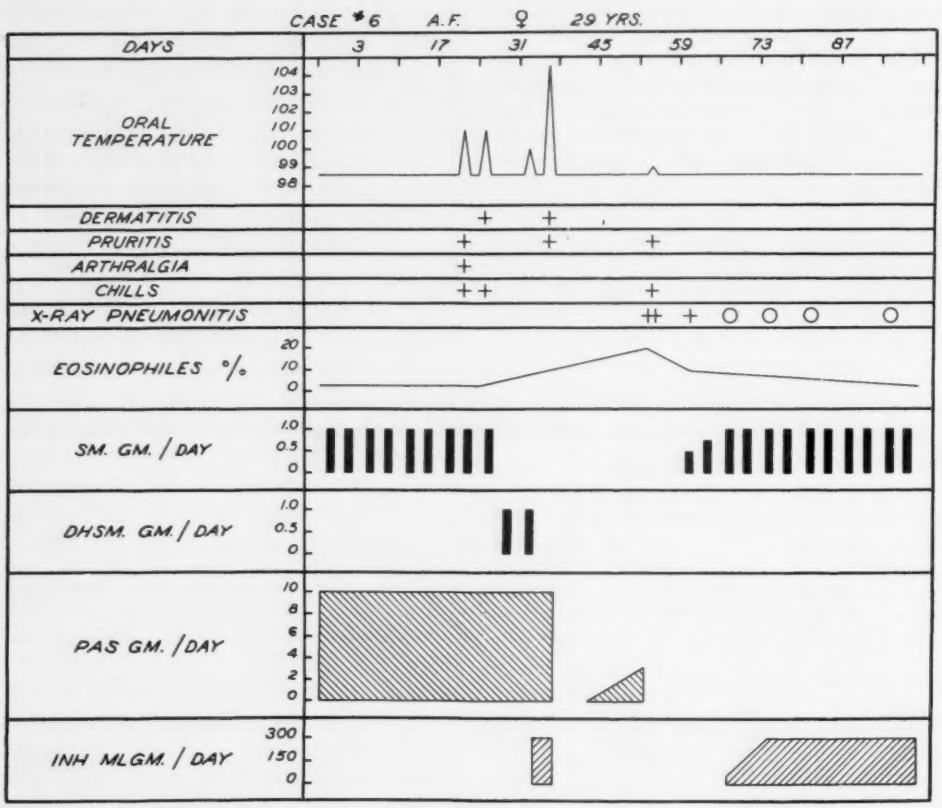


FIG. 3

Fig. 3.—On the line labelled "x-ray pneumonitis" a double or single plus mark or zero appears on each day a chest roentgenogram was made. A double plus indicates a severe acute pneumonitis; a single plus, a less severe pneumonitis, and a zero indicates that a chest film showed no evidence of acute pneumonitis.

10 gm. daily, was started. There was no reaction until May 5, when she developed fever and chills and, the next day, swelling and ulceration of the gums. The PAS was discontinued. On May 8 the total leucocyte count had fallen to 2150 from an admission level of 9450. Differential count showed only 1% neutrophiles. Penicillin 300,000 units was administered twice daily, starting on May 8. Temperature rose to 102 F by May 10, and there was bilateral cervical adenitis. A transfusion of 500 cc. of whole blood was given on that date. Over the next five days the total leucocyte count rose to 5800 and the differential count became normal. The gingivitis and cervical adenitis had subsided by May 15. On Oct. 17, 1950, PAS was again tried, the daily dose starting with 2.5 gm. and gradually increasing. Leucocyte counts were done twice daily at first, then daily, every two days, twice weekly, and, finally, weekly until discharge. No leucopenia developed, and dosage was gradually increased over a two-week period to 10 gm. daily. The drug was continued until discharge without further leucopenia. On Oct. 30 desensitization to streptomycin was attempted, starting with 0.1 gm. and increasing to 1.0 gm. daily on Nov. 8. No reaction occurred until Nov. 13, when temperature of 100.8 F, nausea, and headache developed and streptomycin was again discontinued. There was no leucopenia with this reaction.

Comment.—This patient reacted to both streptomycin and dihydrostreptomycin with chills, fever, and a skin eruption. On PAS alone she developed fever, leucopenia, gingivitis, and cervical adenitis. Desensitization to PAS was successful, but an attempt to desensitize to streptomycin resulted in another reaction with headache, nausea, and fever. Isoniazid was not available at the time she was taking treatment.

CASE 6. (Figure 3).—*Löffler's syndrome, fever, chills, arthralgia, skin eruption*

A. F., a 29-year-old woman who had had a left thoracoplasty, was readmitted with a new minimal lesion in the right upper lobe (Fig. 4). Streptomycin 1 gm. twice weekly and PAS 10 gm. daily were given, starting Dec. 20, 1952. On Jan. 12, 1953, within a few hours of her semiweekly streptomycin injection she had a chill, pain in both upper extremities, and temperature of 101 F. Symptoms had subsided and temperature was normal the following day, but three days later, again following her semiweekly streptomycin injection, she had a chill, temperature of 101 F, and an erythematous rash on chest, abdomen, and arms. PAS was continued, but dihyrostreptomycin was substituted for streptomycin. One week later, on Jan. 22, 1953, the day of her second semiweekly injection of dihydrostreptomycin, she had a third

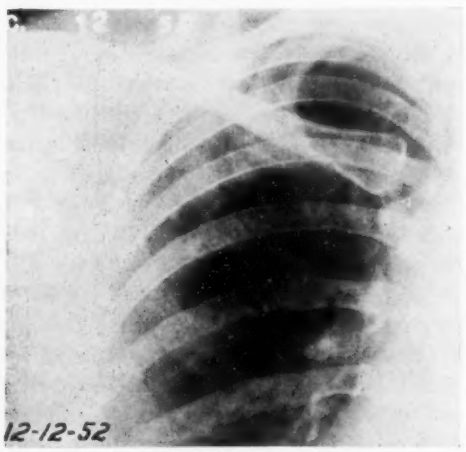


Fig. 4 (Case 6).—Before chemotherapy was begun, showing a minimal lesion in the right upper lung field.

reaction, with temperature of 99.6 F. Dihydrostreptomycin was then discontinued, but PAS therapy was continued, with the addition of isoniazid, 300 mg. daily. The fourth and severest reaction of all occurred at 4 p.m., Jan. 26, 1952, while she was thus taking isoniazid and PAS. With this reaction there was temperature of 104.6 F and recurrence of the skin eruption. Both drugs were discontinued, and symptoms subsided. On Feb. 1 PAS was resumed without isoniazid, streptomycin, or dihydrostreptomycin but in desensitizing doses, beginning with 10 mg. the first day and gradually increasing. On Feb. 12 the dosage of PAS had reached 0.8 gm. four times a day. She then had her fifth reaction, a mild one, with generalized pruritus, chilly sensations, and temperature of 99.0 F. Roentgenograms of the chest that day showed a

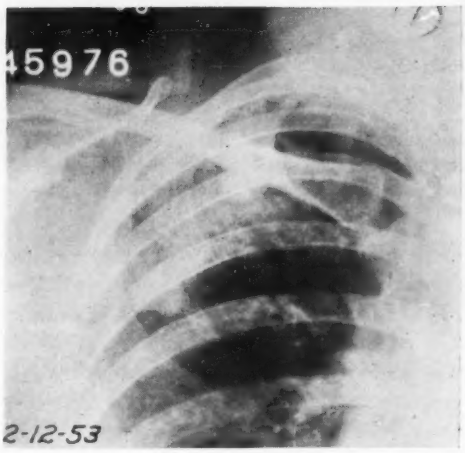
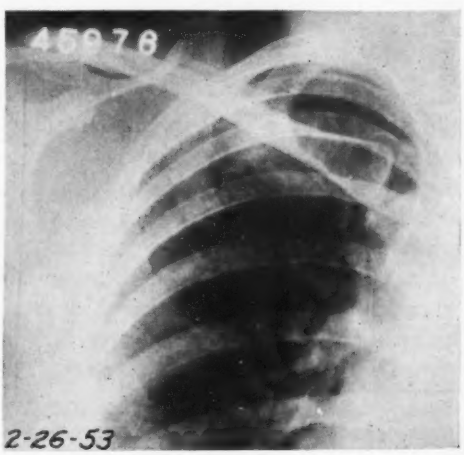


Fig. 5 (Case 6).—During attempted desensitization to PAS, showing new infiltration in the first and second interspaces contiguous with lesion in Figure 4. On the day this film was taken there was an eosinophilia of 20% with chills, pruritis, and elevation of temperature. PAS was again discontinued on this date.

new dense infiltration in the right upper lung field, seen in the first and second anterior interspaces and contiguous with the lesion for which she had been readmitted (Fig. 5). There was a 20% eosinophilia. PAS, which she had been taking alone, was discontinued. Seven days later, on Feb. 19, another roentgenogram showed marked clearing of the new infiltration and there was a drop of the eosinophiles to 10%. Streptomycin was resumed on that date, starting with 0.5 gm., with 0.75 gm. five days later and 1.0 gm. twice weekly thereafter.

Fig. 6 (Case 6).—Complete resolution of the Löffler's infiltration seen in Figure 5, leaving only the minimal lesion which was present before chemotherapy, as shown in Figure 4.



There were no further reactions. By Feb. 26 there was complete clearing of the new infiltration in the right lung (Fig. 6). Isoniazid was added on that date, beginning with 50 mg. once a day and reaching full dosage on March 3. Streptomycin 1 gm. twice weekly and isoniazid 300 mg. daily were continued without further allergic symptoms until the patient's discharge from the sanatorium, on Sept. 30, 1953.

Comment.—This transient pneumonitis, clearing within 14 days, with eosinophilia of 20%, is consistent with Löffler's syndrome. The patient's last reaction occurred while she was taking PAS alone. She was therefore unquestionably allergic to PAS. The first three reactions appeared while she was on PAS combined with twice-weekly streptomycin or dihydrostreptomycin, and each occurred on the day the semiweekly streptomycin or dihydrostreptomycin was administered. One could postulate sensitivity to streptomycin and dihydrostreptomycin as well as to PAS to account for the reactions on the days she was given the two former drugs, and to explain the rapidity with which she reached full dosage of streptomycin in February without reaction—in three graduated doses—one could assume that she had lost her sensitivity to streptomycin in the preceding 55 days during which she did not get the drug. I prefer, however, to consider this, like Case 1, an example of the nonspecific flare-up. An observer in another sanatorium † has reported reactions in PAS-sensitive persons on the days of their semiweekly streptomycin or dihydrostreptomycin injections.

GENERAL COMMENT

Drug eruptions are great imitators, and allergic dermatitis to PAS assumes many forms. Some of the PAS eruptions seen at the Middlesex County Sanatorium have been localized and rapidly clearing, as in Case 3; others, widespread and slow to disappear, as in Case 2. In those which clear quickly when both drugs are discontinued, determination of the responsible allergen can be started immediately. Both streptomycin and PAS were discontinued in Case 3, and after a week the eruption had disappeared. PAS, being more often the cause of sensitization reactions than streptomycin, was presumed to be the exciting agent in this case, and PAS desensitization was begun. When no reaction occurred on increasing dosage and full dosage of PAS was tolerated, streptomycin was then added and continued in full dosage without further reaction. If the rash had reappeared on the addition of streptomycin, dihydrostreptomycin or isoniazid could have been substituted or streptomycin desensitization attempted.

When the eruption clears slowly, the problem is more difficult. To stop chemotherapy altogether and wait weeks or months for the lesions to clear entirely may delay the arrest of the pulmonary lesions or result in their spread. In 1952 the introduction of isoniazid as an alternative therapeutic agent simplified the problem by providing a substitute for an allergenic drug and allowing continuance of combined therapy. PAS is far more frequently the cause of allergic reactions than streptomycin and should be suspected first in the case of a patient getting combined therapy. We have never seen any of these hypersensitivity reactions attributable to isoniazid. Transitory skin reactions,[9] urticaria,[12] and drug fever [13] have been reported, but such reactions to isoniazid are rare. In cases with very active tuberculosis, where the risk of progression of disease is great, PAS can be discontinued and isoniazid substituted, continuing streptomcyin. If the dermatitis gets no better, streptomycin can then be discontinued and dihydrostreptomycin substituted or isoniazid continued alone for long enough to determine whether the dermatitis improves. Bacilli resistant to isoniazid emerge in from 3 to 14 weeks when the drug is administered alone to patients with pulmonary cavities.[9] While the belief that such resistance is always significant and irreversible and involves loss of further benefit from the drug has recently been questioned,[10] most workers will hesitate to administer isoniazid alone to patients with

† Kurzmann, R.: Personal communication to the author.

pulmonary cavities until the subject of isoniazid resistance has been studied further.

Some minor skin reactions can be disregarded without changing drug dosage or can be controlled by antihistamines. Progressing or extensive drug eruptions, however, may become serious and require cautious management. One of our outpatients not included in the case reports had been taking streptomycin and PAS for many months at home, ostensibly under the care of his local physician. He developed an eruption but continued the drugs for another month at home just prior to the admission to the sanatorium which he had previously refused. Both drugs were discontinued at that time, but the eruption, starting on the scalp and postauricular areas, had spread to the arms, forearms, hands, chest, and legs, with scaling, crusting, vesiculation, fissures, and lichenification. These lesions became gradually worse for several months, in spite of antihistamines and local therapy, and overshadowed his pulmonary problem. His pruritis was so severe that cortisone was reluctantly tried, with a concurrent course of isoniazid to prevent the exacerbation of tuberculosis which cortisone so commonly causes. The 14-day course of cortisone 100 mg. daily did not result in a lasting improvement in the dermatitis, which, however, gradually and spontaneously improved and almost entirely cleared five months after streptomycin and PAS were discontinued. The identity of the offending drug was not investigated for fear of lighting up the eruption. On admission, tubercle bacilli grown from the sputum were highly resistant to 200γ/ml. of streptomycin. Such drug eruptions, continuing and progressing for months after exposure to the allergen has terminated, have been frequently described.[11]

Hepatitis in a patient taking PAS should always raise the suspicion of drug hypersensitivity. In the case reported here, the second we have observed, the associated drug dermatitis and arthralgia, with a 7% to 27% eosinophilia, suggested an allergy, although infectious hepatitis could not be ruled out. We considered PAS to be the offender because of the numerous reports of hepatitis from PAS sensitivity. The patient's noncavitary lesion was stable when the hepatic symptoms subsided and has remained arrested without further chemotherapy.

Severe leucopenia appeared in Case 5, but the patient was successfully desensitized to PAS, the responsible drug. Although dangerous, the attempt to desensitize her was justified by her known sensitivity to streptomycin and dihydrostreptomycin, the only other antimicrobials against tuberculosis available at that time.

Transitory pneumonitis with eosinophilia, first described by Löffler,[5] if wrongly diagnosed as a spread of tuberculosis, can result in an unnecessarily prolonged sanatorium treatment or needless postponement of resectional or collapse surgery. If the possibility of Löffler's syndrome is kept in mind, frequent roentgenograms and blood studies will make the diagnosis. The infiltration cleared in 14 days in the case reported here.

SUMMARY

Six cases with allergic reactions to *p*-aminosalicylic acid are reported, including three with drug eruptions, one with hepatitis and monocytosis, one with leucopenia, and one with transient pneumonitis and eosinophilia (Löffler's syndrome). Four of these patients had multiple manifestations of allergy, and some were allergic to streptomycin and dihydrostreptomycin or both as well as to PAS.

Desensitization to PAS was successful in three of these cases, allowing resumption of full dosage and continuance of the drug. With full tolerance of PAS in adequate dosage, streptomycin or dihydrostreptomycin therapy could then be resumed with protection by PAS against the emergence of tubercle bacilli resistant to these drugs.

The management of hypersensitivity reactions to PAS is discussed.

Occasional patients on combined daily PAS and twice-weekly streptomycin therapy, who are hypersensitive to PAS but not demonstrably hypersensitive to streptomycin,

nevertheless can have reactions immediately following the semiweekly administration of streptomycin. This is apparently an example of the "nonspecific flare-up" cited by Sulzberger,[8] in which lesions first produced by one agent may become exacerbated on exposure to another.

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Chloramphenicol in Paratyphoid A

Observations with a Note on the Clinical Aspects of the Disease

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Chloramphenicol (Chloromycetin) at present is the best therapeutic agent available for typhoid. Because it is not the ideal one, some early observers felt that the drug was useful chiefly in the first few days of fever. Given later it presumably controlled the symptoms without significantly influencing the pattern of recovery. Salmonella typhosa may persist in the blood and feces, and relapse may occur during treatment.* It was thought also that early treatment retarded the immune response to infection. The incidence of relapse was unchanged in treated patients and in some instances was actually higher.[3] Nine per cent of Watson's 110 patients responded poorly or not at all to therapy, and toxicity from the drug occurred in 10% in the form of nausea, vomiting, urticaria, and oral moniliasis. Large initial doses seemed to be harmful in severe cases.

Despite the reported shortcomings of antibiotic therapy just mentioned, statistics compiled from large numbers of patients show that chloramphenicol radically alters the outlook in typhoid. Fever usually disappears in three to six days after treatment is started, regardless of the previous duration of disease.† The incidence of complications was reduced from 30% to 10%; the death rate, from 14% to 1.4%, and the average period of hospitalization fell from 42 to 28 days.[5] Chloramphenicol therapy does not retard the serologic response significantly.‡ Taking these advantages into consideration, there is no doubt of the value of chloramphenicol therapy for typhoid. Unfortunately, the rate of relapse is only slightly reduced.

Less attention has been given to the effects of antibiotic therapy for paratyphoid infections, which closely resemble typhoid. Among 400 patients with paratyphoid B, the death rate of treated ones was 0.5% as compared with 1.6% in untreated ones.[5] In other reports, data on paratyphoid A and typhoid were mingled.[3] An unusual opportunity was present in this hospital to study the matter. Paratyphoid A here is next to typhoid in incidence, in a ratio of about 1:3. Records of 105 adult patients for compilation were selected from a much larger number on the basis of completeness of data and of diagnosis proved by the presence of Salmonella paratyphi A in the blood and/or feces. This being a municipal hospital, almost all patients after 1953 received chloramphenicol. Records of untreated patients for controls were gathered mostly from the years 1952 and 1953, when the drug was in limited supply or unavailable. There is no reason to believe that the nature of the disease was different then, and the variety of S. paratyphi A was the same.

The age of patients ranged from 14 to 60 years; most of them were between 20 and 30 years old. Seventy-four were males; 31 were females. The usual diagnostic and general therapeutic measures were applied. Blood and stool cultures were made at admission and weekly thereafter. The agglutinin titers for S. typhosa and S. paratyphi A, B, and C were measured once weekly. Antibiotic treatment in most cases consisted of a single continuous course. On the first day patients received 250 mg. of chloramphenicol every six hours; then, 250 mg. every three hours until two days after the fever disappeared and 250 mg. every six hours for five days

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* References 1 and 2.

† References 2 and 4.

‡ References 2 and 4.

more. There were no shock-like reactions to therapy in severely sick patients as had been observed when large initial doses were given in typhoid.

The records of 52 treated and 53 untreated patients were compared. Since the fever chart is an objective guide to the progress of disease, temperature tracings were superimposed to coincide with the day of disease and show graphically any changes in nature or duration of disease brought about by therapy. To avoid greater confusion in the maze of lines, the tracings of only 37 treated patients were drawn in Figure 1, to compare with those of 37 untreated ones in Figure 4. The end of febrile periods is indicated by solid discs below 37 C. Relapses are drawn in dotted lines until treatment was started and end in the circles.

TREATED PATIENTS

Late entry into the hospital or delay in diagnosis seldom permitted treatment to begin before the fifth day of disease. Most patients were admitted after the 10th day. The temperature tracings in Figures 1 and 2 begin when treatment was started. As shown by the heavy dots below the 37 C line in Figure 1, fever in most of the 37 cases ceased between the 12th and 20th days. Treatment failed in one case in which fever persisted for 25 days. The average length of fever in 52 patients was 16 days, not including relapses. The average duration of fever from the beginning of treatment to recovery was five days. There was a relapse in nine patients, or 17%. Two died.

To see whether treatment is more effective early in the disease Figure 2 was drawn. Among 15 patients in whom treatment was begun before the 10th day, the temperature fell to normal in an average of 5.1 days. The average duration of disease was 13 days. All except one were well by the 15th day. Relapse occurred in three, and one died. Among 15 other patients treated after the 10th day, fever disappeared in 4.8 days. Three had a relapse, and one died.

Cortisone (Cortone) acetate was given to three patients with severe toxemia in doses of 300, 200, 100, and 50 mg. on successive days. In two patients fever and toxemia disappeared within five hours after the first dose. In one of them fever rose to sharp peaks on the third and fourth days of treatment, but without other symptoms except euphoria. The prompt clinical improvement in both was striking. Symptoms abated somewhat in the third patient, but fever was not influenced.

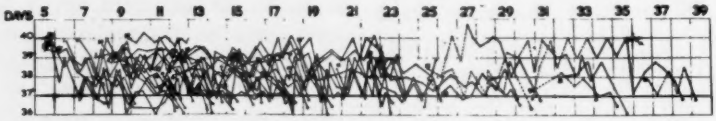

Fig. 1.—Superimposed fever tracings of 37 patients treated with chloramphenicol. Relapses are represented by dotted lines until treatment begins.

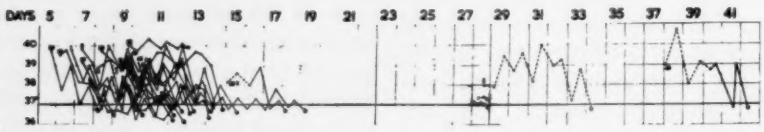

Fig. 2.—Superimposed fever tracings of 15 patients in whom treatment was begun before the 10th day of disease.

UNTREATED PATIENTS

Figure 3 illustrates the duration of fever in 15 patients who entered the hospital before the 10th day of disease but received no chloramphenicol, to be compared with the 15 treated ones in Figure 2. Disease lasted on an average of 19.2 days; in one case, 39 days. Relapse occurred in five. Obviously, care in the hospital without antibiotic therapy failed to modify the disease significantly.

Figure 4 shows the superimposed fever lines of 37 patients, to be compared with those of the 37 treated ones of Figure 1. The density of lines up to the 31st day indicates prolonged illness in many in contrast

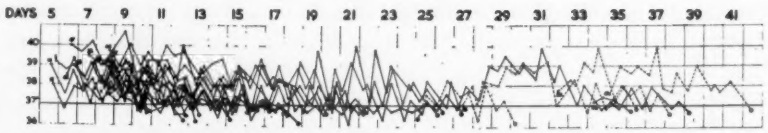

Fig. 3.—Superimposed fever tracings of 15 untreated patients admitted to the hospital before the 10th day of disease, to compare with Figure 2.

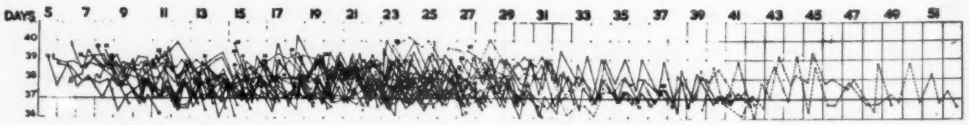

Fig. 4.—Superimposed fever tracings of 37 patients not treated with chloramphenicol, to compare with Figure 1.

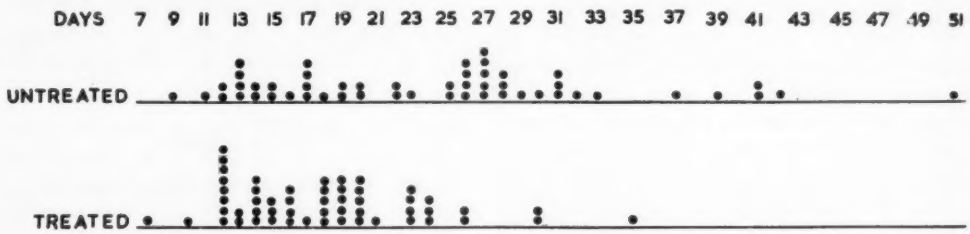

Fig. 5.—Days of recovery of 52 untreated patients and 53 patients treated with chloramphenicol.

with Figure 1. In three cases fever lasted more than 40 days. The average duration of disease in 53 cases was 23.7 days, not including relapses. Ten patients had a relapse (19%), and only one died. For more ease in comparison, the indicated days of recovery for 52 treated and 53 untreated patients are concentrated in Figure 5.

COMMENT

Although paratyphoid A is less severe than typhoid and the death rate is about 1%, the effects of chloramphenicol therapy are similar in each. The results of therapy are almost identical with those reported by Lantin for typhoid, in which the average duration of fever was 16.9 days and fever abated after 4.48 days of treatment.[6] By visual means alone the contrast between Figures 1 and 4 and, especially, between Figures 2 and 3 shows that therapy shortened the duration of paratyphoid A. Figure 5 serves as a summary. Fever lasted on an average of five days whether treatment was begun early or late in the disease. Unfortunately, as in typhoid, treatment did not reduce the incidence of relapse. There was no significant relationship between the height of the agglutinin titer for S. paratyphi A and the occurrence of relapse to indicate interference of therapy with the immune response. Of the nine treated patients who had a relapse, relapse was preceded by a titer of over 1:1600 in the serum of three. No relapse occurred in eight patients in whom agglutinin was not demonstrable. In 10 untreated patients, relapse occurred after the titer had risen to 1:1600 in 6. Chloramphenicol is bacteriostatic, and for unknown reasons the surviving bacilli at times reactivate disease. Relapses responded to therapy like the primary bout. Further study is needed to discover a means to prevent relapse. Serious incidents were surprisingly rare. Hemorrhage occurred in one treated patient, and perforation, in an untreated one.

Evidently, the effect of chloramphenicol on paratyphoid A is not so striking as the effect of antibiotics on certain other infectious diseases. It is of value, however, if it shortens the average duration of disease from 23.7 days in untreated patients to 16

days in treated ones and shortens the period of hospitalization in proportion.

CLINICAL CHARACTERISTICS OF PARATYPHOID A

Opportunity was taken to study the clinical aspects of paratyphoid A as it occurs in the population here and to compare it with typhoid. In general, the characteristics of both conformed with descriptions in textbooks. Paratyphoid A usually is milder than typhoid and has fewer serious incidents and a lower death-rate. Its average duration in untreated patients was 23.7 days. Clinical differences are best brought out when large numbers of cases are studied; isolated cases may be indistinguishable from typhoid. Despite malnutrition and parasitosis of many patients, the mildness of paratyphoid A often was surprising. Even with fever of 38 or 39 C many patients were never very sick. In the hospital records in 32% of cases there is notation of mild illness.

While all clinical details were not always entered into hospital records, the following approximate percentages were gathered: In 75% of cases disease began with fever and chilliness or fever alone. Cough was present in 34% and pulmonary rales in 16%. Constipation was noted in 26%; diarrhea, in 14%. Later in the disease there was relative bradycardia or a pulse rate consistently under 100 a minute in about 50%. The fever, as shown in the Figures, usually was remittent, with large diurnal fluctuation. Eighteen per cent complained of impaired hearing, and the same percentage, of dizziness. Headache was noted in only 10%; nausea and/or vomiting, in 5%. Abdominal pain and distention seldom occurred. Profuse sweating was prominent in 25%, especially toward the end of the course and shortly afterward. The spleen was enlarged and palpable in half the patients; the liver, in 36%. Rose spots were seen in 50%.

In the great majority of cases the leucocyte count varied from 5000 to 7000 per cubic millimeter; the lowest, 3200; the highest, 12,000. In the early stage, the sedimentation rate, measured by Westergren's method, usually was increased, ranging from 10 mm. to 50 mm. after the first hour and 20 mm. and 140 mm. after the second hour. Later, the rate often increased. The fastest rates usually coincided with anemia. In about 20% agglutinin for S. paratyphi A never appeared, and in 20% the titer never rose over 1:200. Ova of Ascaris were present in the feces of about 40%, and those of Ancylostoma, in 18%. Shigella bacilli were present in four patients' feces.

The rarity of serious incidents was mentioned before; there was one hemorrhage and one perforation. Complications in single cases were psychosis, abortion, epistaxis, malaria, amebiasis, and filariasis. The death rate was 3% of 105 cases.

CONCLUSIONS

Chloramphenicol caused the fever in 52 cases of paratyphoid A to decline to normal temperature in an average of five days. It shortened the average duration of disease to 16 days, as compared with 23.7 days in 53 untreated patients. Therapy was effective regardless of the day of disease on which treatment was begun. Therapy did not alter the incidence of relapse, which occurred in about 18% of cases.

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Agranulocytosis Associated with Chlorpromazine Therapy

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Chlorpromazine is proving to be a valuable adjunct in the therapy of many psychiatric and medical disorders. The possibility that occasional persons may develop agranulocytosis while being treated with this drug is not as widely appreciated as it might be.

Chlorpromazine has been used at the University of Minnesota hospitals since the spring of 1954; during this time several hundred patients have received this medication for one or another reason. In addition to those cases in which chlorpromazine was prescribed by us we have seen many patients who have tried this medication before they were referred to us.

The following is our only case so far encountered who has developed agranulocytosis.

REPORT OF A CASE

A 52-year-old white woman was referred to us for the first time on Feb. 1, 1955. She gave a history of becoming increasingly tense and nervous for several months. For a month prior to seeing us she had become discouraged and incapacitated by her agitation and fear of insanity. There was a history of several similar, but milder, episodes in the past. These had always cleared up spontaneously after a few months; the patient had never sought medical care for them and had never been hospitalized. Medical examination on Feb. 1 was essentially negative except for moderate obesity and a blood pressure which varied between 180/110 and 254/140 mm. Hg. The blood cell count was completely normal: the hemoglobin was 16 gm. per 100 cc., and the leucocytes were 8400/cu. mm., with 70% neutrophiles. The psychiatric diagnosis was a depressive reaction in a person with chronic anxiety. Hospitalization and electroshock treatment, both of which were tentatively recommended, were refused; the patient elected to remain at home. She returned on Feb. 11 with the complaint that she was getting no better and asked for something that would give her relief. Chlorpromazine, 50 mg. three times daily, was prescribed. On Feb. 19 she reported that she was considerably less tense and more determined than ever to fight off her illness at home. As she complained of being "dopey," the dosage of chlorpromazine was changed to 25 mg. five times daily. Because the patient lived 160 miles away, she was instructed to report to her family physician for further care. For the next four weeks the patient took chlorpromazine, 25 mg. three times daily, instead of the prescribed five times daily. She was fairly comfortable during this period and did not report to her physician as advised. On March 19, seven weeks after the chlorpromazine was first prescribed, she began to have a sore throat. This became progressively worse, but she did not seek medical care until three days later. At this time she was suffering from severe prostration. The angina had become grave; there was a great deal of induration in her neck. She had difficulty in swallowing and talking.

Medical examination on March 22 revealed an obese white woman in a severely depressed state who was acutely ill. The temperature was 104.8 F; the respiratory rate was 40, and the pulse rate was 116 per minute. The blood pressure was 164/104 mm. Hg. There was slight scleral icterus. The fundi showed normal discs and Grade 2 arteriosclerotic changes, Keith-Wagener classification. The pharynx and the palate were erythematous, with many large pustules and ulcerations. The chest was clear to percussion and auscultation. The heart was slightly enlarged to the left on percussion.

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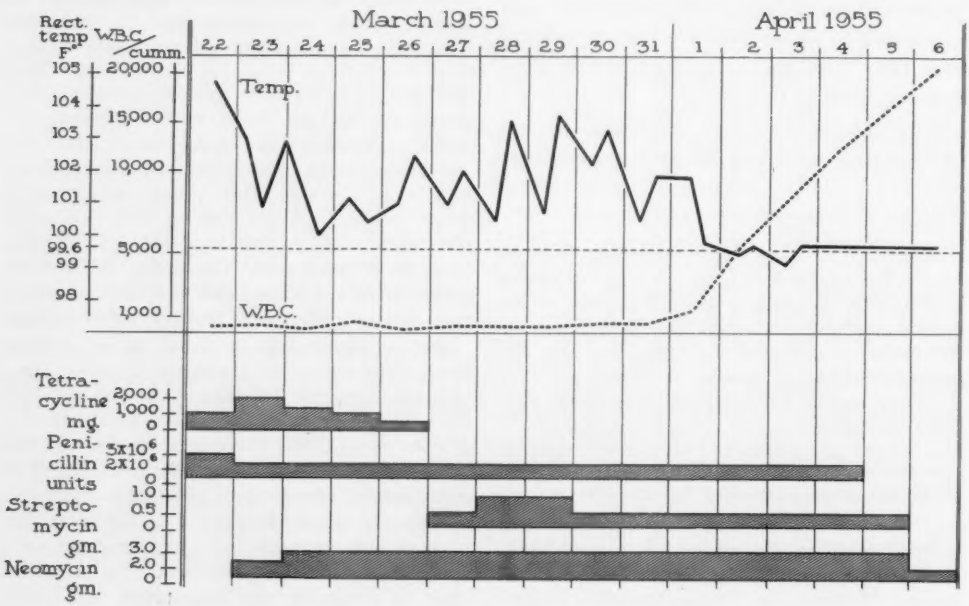
University of Minnesota Hospitals: Fellow in Internal Medicine, Department of Internal Medicine (Dr. Rotstein); Instructor, Department of Internal Medicine (Dr. Frick); Professor, Department of Psychiatry (Dr. Schiele).

A harsh Grade 2 systolic murmur was heard over the whole precordium. The abdominal and the neuromuscular examinations were within normal limits. A film of the chest revealed clear lung fields and moderate left ventricular enlargement. The electrocardiogram was read as abnormal on the basis of nonspecific ST and T wave changes in Leads I and aV_L.

Laboratory studies on March 22: Hgb., 14.2 gm. per 100 cc. Leucocytes, 550/cu. mm., all lymphocytes. One histiocyte and an occasional monocyte were found during intensive search of several slides. The platelet count was 168,000/cu. mm. The erythrocyte sedimentation rate was 90 mm. in an hour. Urinalysis: Specific gravity 1.026, pH 5, albumin 1+, sugar 4+, and a few granular casts in the sediment. The fasting blood sugar was 263 mg. per 100 cc., and the blood urea nitrogen, 23 mg. per 100 cc. Sternal bone marrow aspiration, performed eight hours after admission, showed a hypocellular marrow with a differential count of 42.2% normoblasts, 0.2% neutrophilic precursors, 0.0% eosinophiles, 0.0% basophiles, 50% mature lymphocytes, 4.8% histiocytes, and 2.8% plasma cells. Megakaryocytes and platelets were present in adequate numbers. The increase in lymphocytes was relative to the virtual absence of granulocytes. Blood and cerebrospinal fluid cultures were sterile. Throat cultures grew out alpha and gamma streptococci and pneumococci. Liver-function tests done on the third day of hospitalization (March 24) showed the following: bilirubin, direct-reaction, 1.4 mg. total, 2.8 mg. per 100 cc; thymol turbidity, 2 units; cephalin-cholesterol flocculation, trace, and sulfobromophthalein (Bromsulfalein) retention, 40% after 45 minutes. At this date the fasting blood sugar was 117 mg. per 100 cc.; serum sodium, 142 mEq/L.; serum potassium, 4.0 mEq/L.; the serum chloride, 114 mEq/L., and carbon-dioxide-combining power, 22 mEq/L.

The laboratory data were diagnostic of agranulocytosis, and the history indicated that chlorpromazine was the offending agent. It is true that the patient had used secobarbital (Seconal), 1½ to 3 grains (90 to 180 mg.), for night-time sedation during her recent nervous illness. Also, she had occasionally taken a tablet of a preparation of acetophenetidin, acetylsalicylic acid, and quinine sulfate (Anacin). However, she had made similar use of these medications for long periods of time during her previous nervous spells. There had been no untoward reaction until the recent episode, and thus it does not seem likely that these drugs played an etiological role in the genesis of the agranulocytic reaction. The patient was treated with penicillin, tetracycline, neomycin, and streptomycin, as illustrated in the Figure. She was also placed in isolation in an attempt to avoid exposure to any pathogens which could be transferred to her by visitors, nurses, and doctors. On the sixth hospital day (March 27) the patient developed a severe monilial infection of the mouth. This was successfully treated with fungicidin (mycostatin) sprayed into the oral cavity five times



Course of a patient with chlorpromazine agranulocytosis.

daily. Tetrazet lozenges * were added to the therapeutic regimen in an attempt to lessen the stomatitis. Because of the danger of monilial infestation of the lower gastrointestinal tract, Mysteclin † was given prophylactically, starting on the ninth day. Up to this date the patient remained toxic and febrile. She was able to take liquids only. As indicated in the Figure and in Table 1, the peripheral leucocyte count was constantly below 800/cu. mm. and there was no trace of any neutrophiles on the peripheral smear. A second bone marrow aspiration was performed on March 31. The differential count at this time consisted of 37.7% normoblasts, 33.7% neutrophiles and precursors, 0.0% eosinophiles, 0.3% basophiles, and 28.3% lymphoid cells. Megakaryocytes and platelets were normal. The granulocytes were moderately decreased and were mainly leucoblasts and promyelocytes, with a few myelocytes and occasional metamyelocytes. On the same day the leucocyte count in the peripheral blood was 800/cu. mm., with a differential count of 2% neutrophiles, 81% lymphocytes, 10% monocytes, 4% basophiles, and 3% plasma cells. A comparison with a previous bone marrow study revealed marked increase in the granulocytic series, though the majority were leucoblasts and promyelocytes (Table 2). These findings suggested that a remission might follow. On the 11th day the white blood cells were 1500/cu. mm., with 11% immature and mature neutrophiles. On April 2, the patient became afebrile and her stomatitis and cervical lymphadenopathy subsided. Antibiotics were discontinued gradually over a period of six days. On April 6 (16th hospital day) a third bone marrow aspiration revealed essentially normal findings (Table 2). The leucocyte count in the peripheral blood went temporarily above normal levels and reached a peak of 23,000/cu. mm., with 79% neutrophiles, on the 16th day. Six weeks later it was back down to 5500/cu. mm., with a normal differential count. Recovery was apparently complete. By this time the patient's depression and nervous tension had also improved considerably.

TABLE 2.—*Differential Cell Count of Nucleated Bone Marrow Cells*

	3/23/55	3/31/55	4/6/55
Normoblasts, %.....	42.2	37.7	17.5
Neutrophiles & precursors, %	0.2	33.7	67.0
Eosinophiles, %.....	0.0	0.0	0.0
Basophiles, %.....	0.0	0.3	1.0
Lymphoid cells, %.....	57.6	28.3	14.5

TABLE 1.—*Peripheral Blood Cell Counts*

Date	Hgb., Gm./ 100 Cc.	Leucocytes/ Cu. Mm.	% Neutrophiles	% Eosinophiles	% Basophiles	% Lymphocytes	% Monocytes	% Plasma Cells	Platelets/ Cu. Mm.
2/ 3/55.....	16.0	8400	70	1	0	25	4	0	.....
Chlorpromazine therapy									
3/22/55.....	14.2	550	0	0	0	100	0	0	160,000
3/23/55.....	....	500	0	0	0	100	0	0	.....
3/24/55	....	350	0	0	0	100	0	0	.....
3/25/55.....	10.8	750	0	0	0	100	0	0	204,000
3/26/55.....	....	350	0	0	0	100	0	0	.....
3/27/55.....	....	500	0	0	0	100	0	0	.....
3/28/55.....	....	500	0	0	0	96	4	0	.....
3/29/55.....	....	500	0	0	0	99	1	0	.....
3/30/55.....	....	800	0	0	2	96	2	0	.....
3/31/55.....	....	800	2	0	4	81	10	0	.....
4/ 1/55.....	....	1500	11	0	2	78	9	0	.....
4/ 2/55.....	....	5050	23	0	0	69	8	0	.....
4/ 4/55.....	....	13250	63	0	0	23	14	0	.....
4/ 6/55.....	....	23000	79	0	2	17	2	0	.....

* Tetrazet, Sharp & Dohme. Each lozenge contains 50 units bacitracin, 1 mg. tyrothricin, 5 mg. neomycin sulfate, 5 mg. ethyl aminobenzoate (Benzocaine).

† Mysteclin, Squibb. Each tablet contains 250 mg. tetracycline and 250,000 units fungicidin (mycostatin).

COMMENT

At the beginning of this century Brown [1] and Türk [2] each described a case of idiopathic agranulocytosis. In 1922 Schultz [3] described six cases of a syndrome of unknown etiology characterized by severe pharyngitis, marked prostration, extreme reduction to complete disappearance of the peripheral blood granulocytes, and, in rapid succession, sepsis and death. It was not until this time that general awareness of the syndrome of agranulocytosis became aroused.

This disorder, as thought of at present, is characterized by a fulminating course, fever and leucopenia with pronounced granulocytopenia without significant changes in the erythrocytes of platelets. Owing to the relatively few cases reported before 1922 and the great increase in the number of cases since then, the action of the newer drugs has been implicated. Aminopyrine, when first introduced in this country in 1922 and widely used, was the chief offender. However, after the toxicity of this drug was recognized, the number of cases due to its use decreased. Every year cases of agranulocytosis due to the introduction and use of new therapeutic agents are reported. Dinitrophenol; sulfonamide compounds; barbiturates; quinine; the thiourea derivatives; panaquine (Plasmochin); the antiepileptic drugs, such as trimethadione, methylphenylethyl hydantoin (Mesantoin), phenacemide (Phenurone), and phenindione; the antihistaminics, such as tripelennamine (Pyribenzamine) and methaphenilene; chloramphenicol (Chloromycetin); streptomycin; gold, inorganic arsenic; organic arsenicals; mercurial diuretics; nitrogen mustard, and benzine have been among the drugs implicated.[4]

Six cases of agranulocytosis due to chlorpromazine therapy have been described in the literature reviewed by us. Lomas[5] reported a case of a 69-year-old woman who developed relative agranulocytosis after receiving 6 gm. of chlorpromazine in 21 days. The leucocyte count fell to 680/cu. mm., with 11% neutrophiles. The patient was placed on penicillin for 10 days and then given a course of five injections of 50 mg. of cortisone. Thereafter the leucocyte count returned to normal. Munch-Peterson[6] reported a case of relative agranulocytosis in a 71-year-old woman. After a total of 10.8 gm. of chlorpromazine given in 48 days the leucocyte count fell to 800/cu. mm., with 14% neutrophiles. The patient was treated with folic acid, blood transfusions, and penicillin. Nine days after the initial agranulocytosis the leucocyte count was again normal. Another case of relative agranulocytosis ascribed to chlorpromazine administration was reported by Giacobini and Lassenius.[7] The patient's leucocyte count decreased to 900/cu. mm., 22% of which were neutrophiles, after 40 days of therapy. Penicillin and blood transfusions were used as corrective therapy; recovery occurred after two weeks. However, this latter case of agranulocytosis cannot be ascribed to chlorpromazine with certainty, for an antihistaminic was given concurrently in order to curb any sensitivity reactions. Tasker[8] reported a case of dermatitis, jaundice, and relative agranulocytosis in a patient who had received a total of 5.5 gm. of chlorpromazine in 41 days. The leucocyte count was 900/cu. mm., with 10% neutrophiles. Despite penicillin and oxytetracycline therapy the patient developed lobar pneumonia and died. Prokopowicz[9] described the occurrence of a case of relative agranulocytosis in a 62-year-old woman after 5.8 gm. of chlorpromazine was taken in seven weeks. Despite penicillin and streptomycin therapy, the patient died 36 hours after the onset of agranulocytosis. Hodges and La Zerte[10] reported a case of jaundice, dermatitis, and absolute agranulocytosis in a 67-year-old woman after 1.01 gm. of chlorpromazine had been administered in seven weeks. The patient was given a course of corticotropin after the development of jaundice and prior to the onset of agranulocytosis. Despite oxytetracycline and streptomycin therapy the patient died. A history of severe penicillin sensitivity was present in this patient.

Agranulocytosis may be due to one of three factors. There may be interference with the metabolic processes involved in the production of the granulocytic precursors. Secondly, there may be direct destruction of these precursor cells in the bone marrow. Thirdly, there may be an antigen-antibody reaction which destroys mature and immature granulocytes. It has been suggested by Kracke[11] that the action of eucaine hydrochloride (Benzamine)-containing drugs might be leucotoxic owing to an oxidation product. However, Dameshek and Colmes[12] obtained a strongly positive reaction following the intradermal injection of a mixture

of aminopyrine and blood serum in three patients. Plum [13] has shown that peripheral leucopenia may develop in an interval as short as six hours following the ingestion of aminopyrine. To account for the rapid disappearance of leucocytes one must assume sequestration of the cells or peripheral destruction, either of which is compatible with the immunological concept of agranulocytosis. In the application of immunochemical methods of the demonstration of white cell agglutinins, it appears that the methods of Dausset and his co-workers,[14] Martensson and Vikbladh,[15] and Moeschlin [16] are not refined enough to determine with absolute certainty the immunological cause of a given case of agranulocytosis. Repeated attempts to demonstrate leucocytic agglutinins in the blood of our patient were unsuccessful. The analogy of the present case with the agranulocytosis observed after aminopyrine therapy strongly suggests that the underlying pathogenic mechanism is similar, i. e., it is probably immunological in type.

The most important step in the treatment of drug-induced agranulocytosis is the complete removal of the offending drug. Whatever natural mechanisms and therapeutic agents can be brought into play to combat the agranulocytic syndrome will then be allowed to act. Secondly, the patient must be protected against sepsis. Penicillin and the broad-spectrum antibiotics should be used immediately to stop exogenous infection. Oral neomycin will sterilize the gastrointestinal tract. Fungicidin has proved to be effective in the treatment of secondary monilial infection. In addition, we have used the measure of prophylactic isolation of the patient.

The last measure to be taken is the only controversial one in the therapy of agranulocytosis. Should corticotropin, cortisone, and allied compounds be used? The action of hormonal therapy in agranulocytosis is, as yet, unknown. It has been assumed that there is interference with the mechanism of antigen-antibody reaction. However, recent work by Segal and Herschful [17] and Kass and Finland [18] suggests that the reaction between antigen and antibody is not blocked but rather that the tissue response to such a reaction is altered. Therefore, if with improved laboratory methods a granulocytic agglutinin can be demonstrated an indication for steroid therapy exists. Cortisone has been shown to stimulate the maturation and release of neutrophiles into the peripheral blood. If myelocytic precursors are present in the bone marrow, another indication for steroid therapy exists. However, if the bone marrow is virtually devoid of granulocytic precursors, one cannot expect any response based on this mechanism. Due caution is indicated in the use of hormonal therapy because of the risk of precipitating an overwhelming sepsis. Ragan and his co-workers ‡ have demonstrated experimentally that steroids suppress connective tissue reaction, and, clinically, this is well documented. In a patient without phagocytic protection against bacteremia, the inflammatory process of localizing an infection is one of the few remaining natural defenses against sepsis. Therefore indiscriminate use of steroids may turn a localized infection into a fulminating bacteremia. If there is evidence of areas of localized infection, such as fluctuant lymph nodes, steroid therapy is probably contraindicated. Furthermore, the evaluation of therapy in cases such as the one reported herein presents a real problem. In this instance it was strongly suggested by many observers that cortisone or corticotropin be used, and serious consideration to their administration was given. However, for reasons outlined above, hormonal therapy was deferred. One day after hormonal therapy was to have been started a few granulocytes appeared in the peripheral blood. Two days later the granulocytes numbered 11%. One week later the patient was well. Had cortisone or corticotropin been used at this critical time the dramatic spontaneous remission might have been attributed to its use. The indications and contraindications for steroid therapy must be weighed carefully before these hormones are employed.

‡ References 19 and 20.

Since chlorpromazine is a very useful drug, especially in psychiatric practice, occasional cases of agranulocytosis probably will occur. What can be done to prevent or lessen the incidence of this complication? The cases reported in the literature and our experience suggest that chlorpromazine agranulocytosis occurs within seven weeks after the drug is started. Therefore frequent white cell counts during this period and whenever else indicated would seem to be warranted. Ambulatory patients on chlorpromazine, such as this case herein cited, should be advised to report to the physician at once if any untoward symptoms, especially sore throat and fever, should develop.

SUMMARY

A case of agranulocytosis due to chlorpromazine is described. Complete recovery occurred with conservative therapy 19 days after the onset of symptoms. The mechanisms of the production of agranulocytosis and the therapeutic approach to this disorder are discussed.

Dr. Robert A. Good and Mr. Arthur Page, of the Department of Pediatrics, aided in the immunological studies discussed in this paper.

ADDENDUM

Since this paper was prepared for publication, we have had a second case of agranulocytosis (nonfatal), which developed approximately six weeks after chlorpromazine therapy was started. Details will be published elsewhere.

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Electromyography as an Aid in Clinical Diagnosis

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The use of the electromyograph (EMG) in clinical diagnosis is now firmly established. Its application in human neurological disorders was described in 1938 by Denny-Brown and Pennybacker.[1] It has been, however, only in the past 12 years that the specific value of the instrument has gained widespread recognition.* This field of clinical electromyography has been covered in excellent fashion by Marinacci in his monograph published in 1955. All workers have noted that the EMG is a laboratory instrument which supplements, but obviously cannot replace, accurate clinical examinations.

The technical accuracy of electromyography depends on two primary factors: a trained electromyographer and an instrument of high fidelity. This instrument should consist of a cathode ray oscilloscope, a sensitive sound amplifier, and methods for permanently recording the electromyogram obtained (tape recording and synchronized cameras). A fine monopolar needle electrode inserted directly into skeletal muscle is used to pick up normal or abnormal electrical activity.

It should be emphasized that careful multiple needle insertions must be made in order to examine any particular muscle adequately.

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* References 2-37.

A normal skeletal muscle at rest generates no electrical activity which is recorded by the EMG. If, however, voluntary contraction occurs in this muscle, it is recorded by the EMG as a diphasic spike potential wave form on the oscilloscope and also as a characteristic knocking sound by the loud speaker. If, on the other hand, the muscle is denervated, whether by anterior horn cell disease in the spinal cord, involvement of the motor spinal nerve roots, or by a lesion of the peripheral nerve leading to the muscle, then such a muscle at rest will fibrillate. In the human, a waiting period of about three weeks after injury is necessary before such fibrillations appear. This denervation fibrillation activity cannot be seen through the intact skin but can be picked up only by a needle electrode and is recorded by the EMG as an unmistakably identifiable wave form and clicking sound. This recording of denervation fibrillation potentials is pathognomonic of lower motor neuron disease and largely forms the basis of clinical electromyography. It is important to note that denervation fibrillation continues as long as the muscle remains muscle (until fibrosis or fatty degeneration appears) or until reinnervation of the muscle occurs. If there is partial denervation of the muscle, denervation fibrillation occurs, but, with contraction, a polyphasic wave form appears accompanied by a chugging sound, which is quite different from that seen or heard from the contraction of a normal muscle.

In upper motor neuron lesions, i. e., cephalad to the anterior horn cells, the EMG records no abnormal potentials either at rest or with voluntary contraction.

CLINICAL APPLICATIONS

The EMG proves its value not only by confirming clinical diagnoses but also by

revealing a surprising amount of important information which cannot be detected by any other methods. Many puzzling problems that cannot be diagnosed by ordinary clinical means fall, logically, into their proper classification with information given by the EMG. Below are listed the neuromuscular diseases in which the EMG has proved of distinct value.

Degenerative Diseases of the Spinal Cord

In the early diagnosis of amyotrophic lateral sclerosis, clinical examination may reveal evidences of anterior horn cell damage only in the intrinsic muscles of the hands, whereas electromyographic examination demonstrates denervation fibrillation and fasciculation voltages in the lower extremities as well. Later in the disease, the EMG continues to reveal this widespread anterior horn cell damage, even though it is impossible clinically to demonstrate it in the lower extremities because of the marked pyramidal tract involvement producing a spastic paraplegia. Also, the EMG helps in the differential diagnosis between a cervical spinal cord tumor and amyotrophic lateral sclerosis, both of which may cause an apparently identical picture of focal atrophy of the hands and a spastic paraplegia. The electromyographic finding of diffuse denervation fibrillation and fasciculation potentials in the lower extremities automatically rules out the possibility of a spinal cord tumor, which will only show anterior horn cell involvement at the level of the tumor and not widespread, as will be the case in amyotrophic lateral sclerosis.

The EMG is also of extreme value in the often confusing diagnosis of early progressive muscular atrophy. In this disease, which is one of pure anterior horn cell degeneration, the presence of diffuse denervation fibrillation and fasciculation potentials is common to all the forms, whether the juvenile form of Werdnig-Hoffmann, the bulbar form of Fazio-Londe, the spinal form of Aran-Duchenne, or the peroneal form of Charcot-Marie-Tooth. Often, therefore, a patient exhibiting only a mild focal muscular atrophy, without reflex or sensory changes, can definitely be shown to have a progressive muscular atrophy, rather than some other form of lower motor neuron disease such as peripheral nerve lesions.

The electromyographic findings of lower motor neuron disease are in no way diagnostic of multiple sclerosis, because, obviously, they may be found in any degenerative disease of the anterior horn cells. Often, however, the diagnosis is so obscure that the findings of diffuse patchy areas of denervation fibrillation without fasciculation voltages are of suggestive significance when combined with characteristic, although minimal, clinical findings.

Primary Disorders of the Muscular System

In myasthenia gravis, the EMG reveals the characteristic fatiguing of the involved muscles, as shown by the gradual diminution and final disappearance of voluntary normal motor unit potentials as the muscles are exercised. Also characteristically, after a period of rest, there is gradual reappearance of normal voluntary contraction potentials. The absence of denervation fibrillation confirms that this disease has no lower motor neuron disease component.

Primary muscular dystrophy, whether the pseudohypertrophic type, the facioscapulohumeral type, or the mixed forms, electromyographically reveals normal, although diminished, motor unit potentials and no denervation fibrillation activity. This is of great value in the early differential diagnosis between pure muscular dystrophy and progressive muscular atrophy.

The three forms of myotonia, congenital (Thompson's disease), dystrophic (atrophic), and acquired (Talma's disease), reveal a most pathognomonic and dramatic electromyographic picture. When the needle electrode is inserted into the muscles of the patient suffering from these diseases, there is at once a tremendous burst of what are apparently spontaneous, involuntary, simple motor unit discharges. These wave forms are of high amplitude, are rapid

in frequency, and are accompanied by a high-pitched howling noise over the amplifier. Both the characteristic wave forms and sound from the hyperirritable muscle reach an immediate crescendo, then wax and wane to reach electrical silence within seconds. The slightest touch on the implanted needle electrode sets off an immediate repetition of this phenomenon. No denervation fibrillation voltages are seen, which places the myotonias in the category of a primary muscular disorder. Voluntary contraction produces normal diphasic wave forms which persist for a period after the patient attempts to relax the muscle.

Patients suffering from disease such as myokymia and periodic familial paralysis have no evidence of lower motor neuron disease electromyographically.

Infectious and Inflammatory Diseases of the Spinal Cord

In anterior poliomyelitis, the electromyographic examination of specifically affected muscles can give important diagnostic and prognostic information. For instance, if one of these muscles, after an appropriate period of time following the onset of the disease, persistently shows complete denervation and, with voluntary effort, no discrete motor unit potentials, then this muscle is hopelessly denervated. This allows early surgical correction and prevents futile and expensive physical therapeutic treatments. Oftentimes, however, because of psychologic factors, a patient may believe a muscle to be completely paralyzed, but, when he is shown by means of the sensitive EMG that when he tries to contract the muscle there appears on the screen and through the amplifier the unmistakable evidence of muscular activity, then reeducation is greatly facilitated.

The EMG is of similar diagnostic and prognostic value in other infections or inflammatory diseases of the spinal cord such as Guillain-Barré syndrome, bacterial infections, either diffuse or focal, and tabes dorsalis.

Neoplasms Involving the Spinal Cord

Tumors involving the spinal cord, other than intramedullary, almost always involve the spinal nerve roots, producing segmental denervation fibrillation. Thus, as has been mentioned, the differential diagnosis between a high extramedullary cervical cord tumor and amyotrophic lateral sclerosis can be facilitated by finding, in the latter, evidence of diffuse lower motor neuron disease in the lower extremities and often in the muscles of the face.

An extradural tumor may often be difficult to differentiate clinically from a spinal nerve root compression syndrome or a specific nerve plexus lesion. Here the EMG, in the case of an extradural tumor, will reveal, usually, the bilateral involvement of more than one nerve root, as shown by denervation fibrillation over the distributions of both the posterior and anterior primary divisions of the nerve roots. In the case of spinal nerve root compression, often caused by a protruded intervertebral disc, the posterior and anterior primary divisions are also involved. Almost always, however, only one specific nerve root is affected. In plexus lesions, the muscles supplied by the posterior primary divisions of the spinal nerve root cannot be involved, since the plexuses are peripheral to the point of origin of these posterior primary divisions. Thus a clear-cut differential diagnosis can be established.

The Spinal Nerve Root Compression Syndrome

Perhaps the commonest and most practical clinical use of the EMG is as an aid in the diagnosis of a compression lesion of a specific nerve root (most frequently by a protruded intervertebral disc). The addition of electromyographic localization to the evidence supplied by the clinical examination and pantopaque myelography results in an accurate and precise diagnosis of the involved nerve root. The basis of the electromyographic localization of a single nerve root lesion is the finding of denervation fibrillation in those muscles supplied by that specifically involved nerve root and in no other muscles. In other words, although an

isolated muscle may have multiple nerve root innervation it will show denervation fibrillation in common only with those other muscles that are innervated by the same compressed nerve root. To illustrate how a lesion compressing, for example, the seventh cervical nerve root may be localized by a process of elimination, the needle electrode is first placed in several areas of the deltoid and biceps muscles, innervated by the fourth, fifth, and sixth cervical nerve roots. No denervation fibrillation voltages are found. Next, the electrode is inserted successively in the extensor carpi radialis, extensor communis digitorum, extensor carpi ulnaris, and the flexor carpi ulnaris (innervated by the sixth, seventh, and eighth cervical nerve roots). In these muscles, a maximum of denervation fibrillation voltages are noted. The next muscle tested is the abductor digiti quinti, innervated by the eighth cervical and first dorsal nerve roots. As in the first instance, no evidence of denervation is found in the muscle. The lesion, therefore, since we have demonstrated that the fifth, sixth, and eighth nerve roots are not involved, must be compressing the seventh cervical nerve root. Examination of the erector colli musculature reveals segmental denervation fibrillation, which confirms the fact that the lesion must involve the posterior primary division. In other words, the nerve root must be involved.

Using the same deductive method, a specific lumbar nerve root lesion can be diagnosed. To illustrate this, let us assume that the first sacral nerve root is compressed by a herniated nucleus pulposus. As in the case of the cervical nerve root lesion, a definite sequence of muscle testing is followed. The needle electrode is placed successively into several areas of the quadriceps femoris (L-2, L-3, and L-4), and no evidence of denervation is found. Progressing, the tibialis anticus (L-4, L-5) is thoroughly sampled, and, again, no denervation fibrillation voltages are picked up. However, in the extensor hallucis longus, extensor digitorum longus, and peroneus longus (L-5 and S-1) a considerable amount of denervation fibrillation voltages is demonstrated. Similarly, in the gastrocnemius (L-5, S-1, and S-2) and the soleus (S-1 and S-2) the EMG reveals evidences of denervation. Since we have demonstrated that the muscles supplied by the fourth and fifth lumbar nerve roots are not involved, whereas the muscles partially innervated by S-1 are, the lesion must be compressing this root. Finally, denervation is found in the erector spinae group which is segmentally innervated by the posterior primary divisions, thus proving that the root and not a portion of the lumbosacral plexus is implicated.

Lesions of the Nerve Plexuses

The commonest lesion involving the brachial plexus is the so-called anterior scalene syndrome. This syndrome is often difficult to differentiate from a lesion involving a single cervical spinal nerve root. This difficulty often can be overcome by careful electromyographic examination of the muscles of the neck and involved arm. Thus, the EMG will show in the case of compression of the brachial plexus by either a tight anterior scalene muscle or by a cervical rib, or both, diffuse denervation fibrillation of the musculature supplied by the plexus and not of the posterior muscles of the neck. On the other hand, in the case of a single cervical nerve root lesion, the EMG will reveal denervation fibrillation confined only to the muscles in the arm supplied by this specific nerve root plus segmental denervation of the posterior muscles of the neck innervated by the involved posterior primary division. It should be pointed out that often the symptoms of an anterior scalene syndrome are largely due to arterial compression and not nerve compression. In this instance, the EMG will reveal little or no evidence of lower motor neuron disease.

A similar deductive method is used in the diagnosis of lumbosacral plexus lesions.

Lesions of the Cranial Nerves

Bell's palsy is the commonest lesion of a motor cranial nerve in which the EMG is

used as a diagnostic aid. If complete denervation fibrillation is found in all the muscles supplied by a facial nerve and if, with voluntary effort, no motor unit potentials are found, then complete physiologic interruption of the nerve can be diagnosed. Conversely, if voluntary motor unit voltages are found from any part of the affected muscles, no matter of how small amplitude, then, despite the clinical impression of complete paralysis, it is possible to state that at least a portion of the nerve is still intact and to predict that some spontaneous recovery will occur. This is, of course, of great psychological value to the patient with unilateral facial paralysis.

In the differential diagnosis between compressive lesions of the high cervical cord, such as by tumors or an Arnold-Chiari deformity, and amyotrophic lateral sclerosis, the finding of denervation fibrillation in the facial musculature helps to rule out the former.

Lesions of the Peripheral Nerves

The electromyograph reaches its highest degree of accuracy in the diagnosis and prognosis of peripheral nerve injuries. A completely severed peripheral nerve will show, approximately 18 days after injury (in the human), denervation fibrillation voltages from all areas of the muscles tested. In addition, no discrete motor unit voltages are produced from any portions of the affected muscles by voluntary contractions. The only bioelectrical sign seen during such voluntary activity is a disturbance of the cathode ray base line, which is a result of motor unit contractions arising from adjacent muscles not innervated by the same nerve, and, with experience, this can be clearly recognized. Thus, a confident opinion can be expressed by the electromyographer that complete interruption of the nerve exists.

Immediately, therefore, the surgeon can reapproximate the severed ends without undue delay. This is of paramount importance, since there is an inverse relationship between a prolonged interval before suture and the effectiveness of the results.

After a nerve suture has been done, and after an appropriate waiting period for nerve regeneration to occur, beginning motor unit contractions are seen in the paralyzed muscles. The frequency and amplitude of the denervation fibrillation voltages gradtually diminish, and the cathode ray baseline disturbance is replaced at first by complex (or polyphasic) motor unit contractions of very low amplitude and frequency; finally, simple motor unit contractions begin to appear. These electromyographic phenomena can be seen long before clinical evidence of motion occurs and assure the surgeon that his nerve suture is intact and that reinnervation is occurring.

With use of a mean rate of 2.5 mm. a day for neurotization and 1.7 mm. per day for maturation (complete myelinization), a table has been constructed which makes it possible to determine the approximate time interval before EMG evidence of regeneration appears. If, after this appropriate waiting period, which is markedly shorter than the usual period of clinical waiting, no EMG evidence of regeneration of the nerves is demonstrated, immediate reexploration should be carried out. Again, the neurosurgeon is afforded the earliest opportunity to establish the continuity of the nerve and, thus, forestall further atrophy of the affected muscles.

In partial nerve injuries, despite the clinical evidence of complete paralysis, the EMG enables the examiner, on finding motor unit contractions, to state that intact nerve fibers exist and, therefore, that the chances of spontaneous regeneration are good.

PITFALLS IN ELECTROMYOGRAPHY

Electromyography, depending upon a mechanical diagnostic instrument, is subject to errors arising, first, from lack of skill or thoroughness on the part of the examiner; second, from incorrect interpretation of the electromyogram, and, third, from the fact that there are anatomic variations of motor nerve supply just as are seen in the sensory distribution.

As we have previously emphasized, the technique of multiple electrode insertions and extensive sampling of the skeletal muscles must invariably be carried out. There is often a tendency on the part of the electromyographer to limit his efforts because of the discomfort to the patient, and he may thus fail to discover significant evidences of lower motor neuron disease.

Considerable experience is required on the part of the electromyographer in interpreting certain aberrant wave forms which may arise at the time of insertion or motion of the needle electrodes, from outside electrical interference, or from the normal contraction potentials of certain small muscles such as those of the face, which may be confused with denervation fibrillation voltages.

A major source of confusion arises in surveying certain patients who demonstrate widespread lower motor neuron disease in spite of the fact that they clinically have only a localized lesion. We feel that these patients may have suffered in the past from some unrecognized disease of the nervous system, such as subclinical poliomyelitis, and thus retain evidences of lower motor neuron disease. In older patients, this confusion also arises occasionally because of circulatory insufficiency which results in damage to the anterior horn cells. In these cases, the electromyographer must utilize his clinical knowledge in interpreting the EMG findings.

In addition, the needle electrode may be inserted inadvertently into one of the many fine nerve fibers which course through the muscles. If this occurs, the patient will complain of increased sharp pain, and there will appear on the electromyograph a rapid burst of even negative spike potentials, with a fast, machine-gun-like sound. A nerve stimulator can be incorporated with the EMG which causes very visible local contractions of the muscle if the electrode is in contact with a nerve fiber. It can be used to rule out this artifact.

SUMMARY

Accurate electromyography can only be accomplished by the combination of a skilled electromyographer and a precision instrument of the highest fidelity.

The EMG is a valuable aid in the clinical diagnosis of such neurological disorders as diseases involving the anterior horn cells of the spinal cord or lesions of the spinal nerve roots, plexuses, and peripheral nerves. The finding of denervation fibrillation potentials in the muscles supplied by these elements of the nervous system is pathognomonic of lower motor neuron disease and is thus of great assistance in clarifying the differential diagnosis of puzzling neurological disorders.

The EMG is also of distinct value in diagnosing primary muscular diseases such as the muscular dystrophies, the myotonias, and myasthenia gravis.

If the evidence supplied by the EMG is correlated with the information obtained by clinical examination, earlier and more accurate diagnoses of neuromuscular diseases can be made.

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Control of Nausea and Vomiting with Chlorpromazine

Incidence of Side-Effects

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Nausea and vomiting are distressing symptoms which denote irritation or abnormal stimulation of the vomiting center, which lies in the medulla oblongata. Etiological factors are diverse and may influence the emesis center directly or, perhaps more frequently, the chemoreceptor trigger zone, which lies more superficially in the medulla.[1]

Of the many drugs which have been advocated to prevent or control emesis, none has achieved such a universal acceptance in a short period as chlorpromazine. It has given clinical protection in apomorphine-induced vomiting,[2] in uremia,[3] in irradiation sickness,[4] in postoperative vomiting,[5] and in several miscellaneous conditions, including the vomiting of pregnancy.[6] Experimental evidence suggests that chlorpromazine exerts an action directly on the chemoreceptive trigger zone.[7] The only dissenting voice against the reliability of chlorpromazine in controlling nausea and vomiting has come from an experienced group who state it gave no significant protection in motion sickness.[8]

Before such a drug as chlorpromazine can be recommended without hesitation, it must not only relieve emesis in a majority of patients; it must also display minimal side-actions which might interfere with the immediate or eventual *status quo* of the patient. It was with both these ideas in mind that the following work was begun.

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From the Division of Anesthesiology, Duke Hospital and University School of Medicine.

Read before the Section on Gastroenterology and Proctology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

CLINICAL INVESTIGATION

In the postoperative period, nausea and vomiting may be instigated by one or several factors. Anesthetic and narcotic drugs may irritate the gastrointestinal tract or stimulate the vomiting center directly. Intra-abdominal surgery may stimulate reflex pathways which will initiate vomiting. Undue motion in the recovery period will precipitate vomiting in a manner similar to that which is seen in motion sickness. Hypoxia during the operative period may lead to emesis, and in some patients gross electrolyte imbalance may be present postoperatively. With these several potential precipitating causes of emesis present after operation, coupled with the fact that patients could be watched carefully for untoward effects, it was felt that chlorpromazine could be given a critical trial in this situation.

Previous work in this field had given some bases for comparison. In a study already reported [9] it was determined in 2000 control patients that the postanesthetic incidence of vomiting in Duke Hospital was 27.2%. In a series of 1000 patients treated with an antihistaminic piperazine derivative, cyclizine hydrochloride (Marezine), the incidence of vomiting was 20.7%. The reduction in vomiting was of statistical significance ($p<0.01$). The side-effects associated with the cyclizine-hydrochloride-treated group were nil. No ill-effects were seen at the site of injection; the recovery time of treated patients was not delayed, and no deleterious effects were noted in the respiratory, cardiovascular, or other systems of the body.

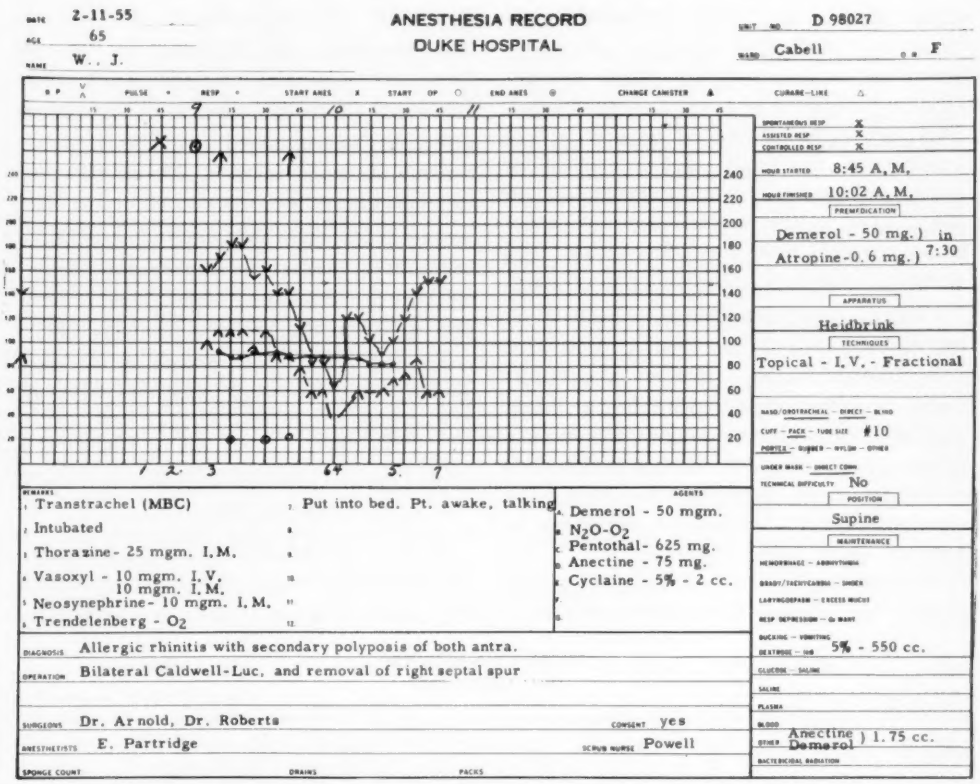

Fig. 1.—Marked hypotension under general anesthesia following chlorpromazine, 25 mg., i. m. Temporary response to methoxamine, more adequate response to phenylephrine (Neo-Synephrine).

The original plan was to administer chlorpromazine to 1000 consecutive patients during anesthesia, about 30 to 60 minutes prior to the conclusion of the surgery. A dosage of 25 mg. given intramuscularly was chosen for adults, as it was the clinical impression, supported by others,[6] that an adequate effect might not be obtained with smaller amounts.

On the first, and actually the only, day in which this dosage was administered, the results were somewhat dramatic. Sixteen patients between the ages of 6 and 67 were given chlorpromazine intramuscularly. Four of these patients vomited in the postoperative period, all after receiving ether anesthesia. The disturbing phenomenon concerning these patients was that nine developed a fall in blood pressure of 40 mm. systolic or more in the recovery room and two had a fall between 20 and 40 mm. systolic, while five showed no adverse cardiovascular effects. Figure 1 is the anesthetic record of one of these patients, a 65-year-old man, normal blood pressure 170/110, who underwent a bilateral Caldwell-Luc operation under orotracheal thiopental (Pentothal), nitrous oxide-oxygen, meperidine anesthesia. After chlorpromazine the blood pressure fell to 60/? and then responded temporarily to methoxamine and with more benefit to phenylephrine (Neo-Synephrine). However, in the recovery room, the blood pressure fell again to 78/50 and remained in this range for five hours, with brief respites being afforded by phenylephrine intramuscularly. Although the patient was awake when leaving the operating room, he became drowsy in the recovery room and was difficult to

arouse during the period of hypotension. In spite of the shock-like levels of blood pressure, the skin remained warm and dry and the peripheral pulse was slow and full. This patient was typical of those in whom hypotension was seen. The consternation caused to surgeons, anesthesiologists, and nurses alike by this unusual trend of events in the recovery room precluded further trial of chlorpromazine in this manner and dosage.

Perhaps we should have been forewarned concerning this hypotensive effect associated with chlorpromazine, since in a previous study on 185 selected patients it was found that 13% developed a fall in blood pressure of 40 mm. or more systolic after intravenous or intramuscular injection.[10] Figure 2 is an example of such hypotension occurring in a patient under spinal analgesia.

After reassessment of the situation, it was decided to reinstitute the study but to reduce the dosage of chlorpromazine to 12.5 mg. intramuscularly and to limit the trial to "good risk" normotensive patients. One hundred such patients have been evaluated. Vomiting has occurred in 15% of these patients, as apposed to 27.2% in the consecutive controlled series. Even in this dosage hypotension following administration has been a problem in 30 patients. Of significance also has been the prolonged drowsiness noted in the patients receiving chlorpromazine. This delay in waking increases the possibility of respiratory complications and extends recovery-room care.

MECHANISM OF ACTIONS OF CHLORPROMAZINE

As more investigation proceeds, it appears that chlorpromazine has a definite depressant effect on certain functions of the hypothala-

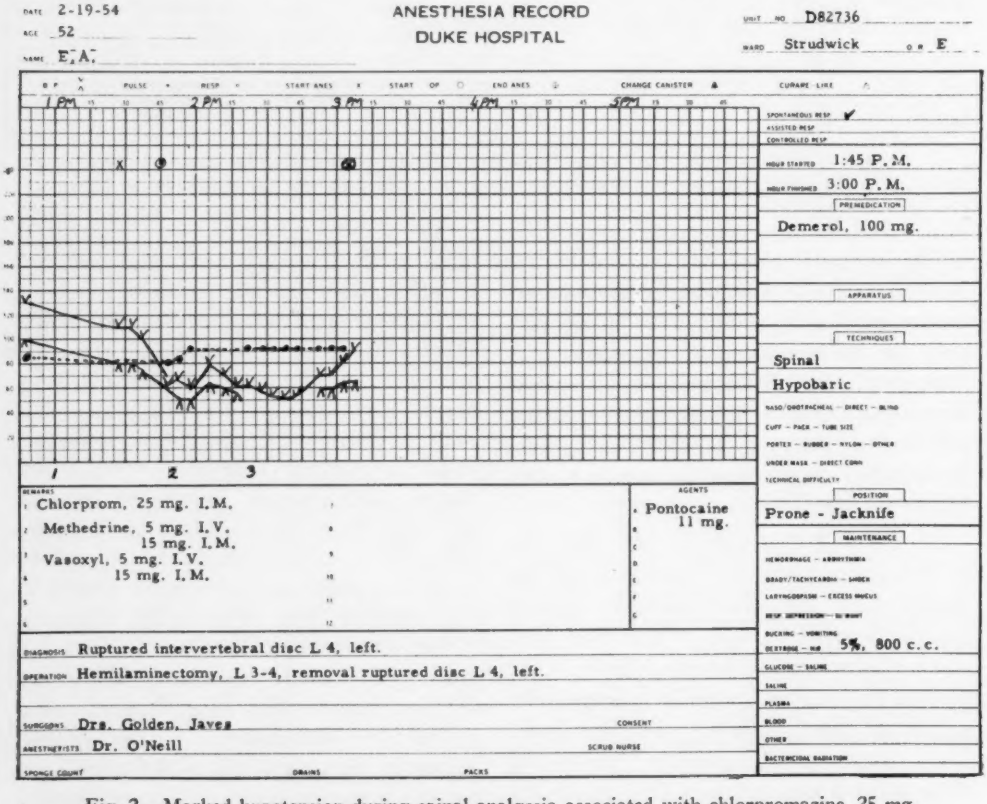

Fig. 2.—Marked hypotension during spinal analgesia associated with chlorpromazine, 25 mg., i. m. Lack of vasopressor response to methamphetamine (Desoxyephedrine) and methoxamine.

mus, midbrain, and medulla.* Experimental and clinical evidence indicates that depression of the chemoreceptor trigger zone or emetic center is only one of the important actions of this versatile drug. The concurrent development of hypotension, drowsiness, and potentiation of narcotic and anesthetic drugs supports this wider concept clinically.

Of practical importance in the routine use of this medication is its effect on the cardiovascular system. Several investigators † have emphasized the hypotensive actions and have indicated that these are due partly to a direct effect on the vasomotor center and partly to a peripheral adrenolytic action. It is impossible to predict which patients will show this tendency to hypotension after either oral or parenteral administration. Marked falls in blood pressure are undesirable in any patient. In those with hypertension or myocardial disease grave results may ensue. Owing to the adrenolytic effect of chlorpromazine, only the more potent vasopressor drugs, phenylephrine and levarterenol, are active in raising the pressure.[10] Figure 3 shows ineffective action of methamphetamine (Desoxyephedrine) followed by the beneficial use of phenylephrine.

Of considerable significance also are the actions of chlorpromazine in producing obstructive jaundice and agranulocytosis,‡ usually after multiple administrations. These late complications of therapy indicate as yet unexplained peripheral actions of the drug.

COMMENT

Whatever the precipitating cause of emesis, stimuli must travel centrally to irritate

* References 11-14.

† References 15-17.

‡ References 18 and 19.

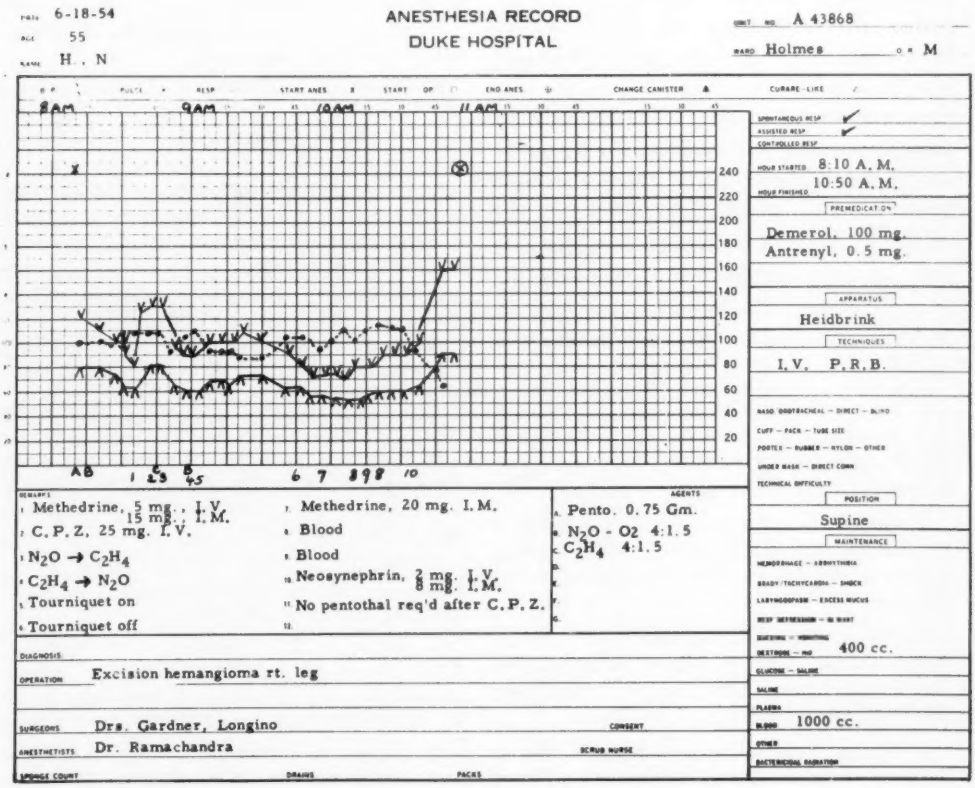

Fig. 3.—Methamphetamine (Desoxyephedrine) at (1) gave anticipated response. Chlorpromazine, 25 mg. i. v., was given at (2). Lack of response to methamphetamine is shown at (7). Adequate response to phenylephrine (Neo-Synephrine) is shown at (10).

the chemoreceptor trigger zone or vomiting center in the medulla. Many different drugs have been recommended to control these symptoms, but none has proved entirely satisfactory, either because it does not relieve vomiting in the majority of patients or because its side-actions limit its safe and universal applicability.

Chlorpromazine is one of the most recent drugs being utilized to control emesis. The preponderance of reports indicates that it is the most effective compound yet presented to the medical profession for this purpose. At the same time, it is being shown that the action of this drug is widespread in the central nervous system and peripherally. Some of these actions, called side-effects as far as control of vomiting is concerned, may jeopardize the vital functions of the patient. For these reasons, it is questionable whether chlorpromazine should be given in a routine fashion to any patient with symptoms of nausea and vomiting, even after a diagnosis is established. It is doubtful whether this drug should be given prophylactically to prevent vomiting, as during the postoperative period. In any situation, the seriousness of the vomiting to the welfare of the patient should be weighed in balance with the possible side-effects which may accrue from the multiple actions of the drug, and then a decision can be made concerning its administration.

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Hepatic Function Studies in Lymphogranuloma Venereum

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Hepatic function has been studied in a number of diseases in which the liver is not primarily involved.* The present report is one of a series of studies on the incidence and significance of abnormal hepatic function in systemic disease.†

Hyperglobulinemia is frequently found in such diseases as rheumatoid arthritis,[14] subacute bacterial endocarditis,[15] sarcoidosis,‡ systemic lupus erythematosus,§ malaria,[12] kala azar,[20] and multiple myeloma.[10] Abnormality of flocculation tests of hepatic function in this group of diseases presumably represents alteration of plasma proteins rather than actual hepatic dysfunction.‖ Since lymphogranuloma venereum is also characterized by hyperglobulinemia,¶ the present study was undertaken in an attempt to determine the incidence of abnormal hepatic function tests in this disease, as well as to determine whether these abnormalities are due to real or apparent liver involvement. The few reports # which have appeared present conflicting views in supporting or denying hepatic involvement in patients with lymphogranuloma venereum.

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Department of Medicine, Veterans Administration Westside Hospital, and University of Illinois College of Medicine.

* References 1-4.

† References 5-13.

‡ References 16 and 17.

§ References 13, 18, and 19.

‖ References 3, 4, 21, and 22.

¶ References 15 and 23-30.

References 25, 29, and 32.

METHODS AND PROCEDURE

Fourteen patients with lymphogranuloma venereum were studied. The criteria for diagnosis were a clinical picture compatible with one of the acute forms of the disease,[33] a positive skin reaction to

TABLE 1.—*Clinical and Laboratory Data of Fourteen Patients with Lymphogranuloma Venereum*

Patient	Hepatomegaly	Frei	Complement Fixation	VDRL*	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Thymol Turbidity, Units	Cephalin Flocculation	Bilirubin, Mg./100 Cc.	Sulfobromophthalein, %	Alkaline Phosphatase
D. G.†	+	+	1:80	Neg.	4.1	5.3	11.0	0	...	3.5	3.6
R. B.	0	+	1:100	Neg.	4.3	5.0	9.7	4+	0.8	3.5	3.0
F. R.	0	Neg.	1:80	Pos.‡	4.1	3.4	1.2	0	0.3	2.5	4.0
A. J.†	0	+	1:80	Neg.	4.3	4.5	2.6	0	...	6.5	2.9
J. D.	0	+	1:80	Pos.	4.5	4.0	4.7	0	...	1.5	4.3
E. A.†	0	+	1:80	Pos.‡	3.6	5.8	10.3	4+	1.3	1.5	4.5
E. H.†	0	+	1:512	Neg.	3.9	3.9	5.0	0	0.7	7.5	2.5
O. I.	0	+	.....	....	3.6	4.5	12.2	4+	0.8	1	...
L. B.	0	+	.....	....	3.9	3.8	6.5	2+	0.7	2	...
J. L.	0	+	.....	....	4.0	4.1	9.2	3+	0.9	7	...
A. W.	0	+	.....	....	3.9	2.9	1.1	1+	0.5	8	...
M. Mc.	0	+	.....	Neg.	4.2	4.9	...	...	...	...	...
A. G.	0	+	.....	Neg.	2.5	4.1	...	...	...	...	...

* Serological test for syphilis.
† Liver biopsy performed.
‡ Reverted to negative with therapy.

TABLE 2.—*Incidence of Abnormal Laboratory Results in Lymphogranuloma Venereum*

Test	Abnormal Value	Cases, No.	Abnormal Results		Range of Abnormality	Remarks
			No.	Per Cent		
Frei	.....	14	13	92.8	.....	The patient with negative Frei test had a positive complement-fixation test
Complement fixation	.....	7	7	100.0	1:80-1:512	
VDRL*	.....	10	3	30.0	.....	In 2 patients the positive tests reverted to negative after therapy
Albumin	<4.0 gm.	14	7	50.0	2.5-3.9	
Globulin	>3.0 gm.	14	13	92.8	3.1-5.8	
Thymol turbidity	>4.0	11	8	72.7	4.7-12.2	
Cephalin flocculation	3+	11	4	36.3	3+-4+	
Bilirubin	>1.0	8	1	12.5	1.3	
Sulfobromophthalein	>4%	11	4	36.3	6.5-8.0	
Alkaline phosphatase	>4.0	7	0	0	.....	Three had levels of 4.0-4.5 units
Liver biopsy	.....	4	..	....	.....	Slight focal inflammation, moderate change in parenchymal cell cytoplasm (see text)

* Serological test for syphilis.

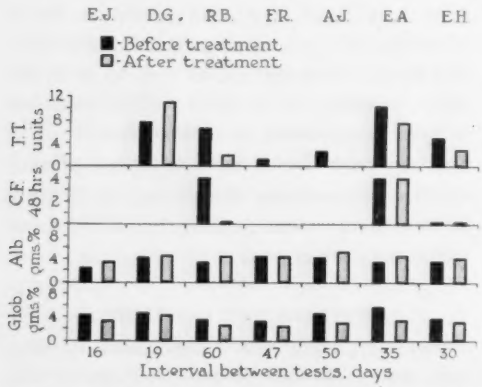

Fig. 1.—Serum proteins and flocculation tests before and after treatment of lymphopathic venereum.

the Frei antigen,[34] and/or positive complement fixation for lymphogranuloma venereum.[33] Biopsy of the liver was performed in four patients, with use of the Vim-Silverman needle. Hepatic function was studied by the sulfobromophthalein (Bromsulphalein)-excretion test by the method of Mateer and his associates[35]; the thymol turbidity, by the procedure of Maclagan[36] as modified by Shank and Hoagland[37]; the cephalin-cholesterol flocculation, by Hanger's method[38] as modified by Neefe and Reinhold[39]; the serum bilirubin, by Malloy and Evelyn's[40] modification of the Van den Bergh method; the alkaline phosphatase, by the method of Bodansky,[41] and the total serum proteins and albumin and globulin levels by a modification of the method of Howe.[42] The upper limits of normal for these tests are shown in Table 2.

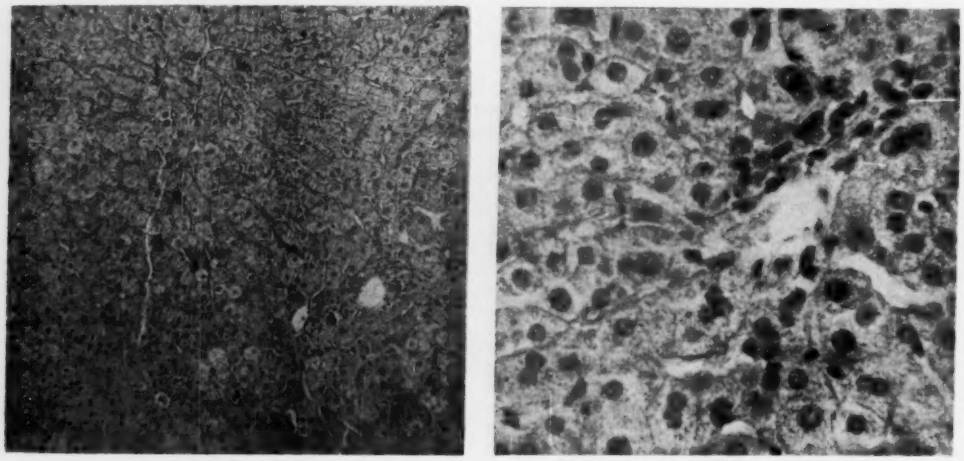

Fig. 2.—*A*, characteristic fields of liver biopsy specimen, showing slight cellular abnormality and portal infiltration; reduced from mag. × 200. *B*, cellular abnormality and polynucleation; reduced from mag. × 400.

RESULTS

The results of liver-function tests performed on the 14 patients are shown in Table 1. The incidence of abnormal results and the range of abnormalities are listed in Table 2. Four of eleven patients had minimal dye retention. The thymol-turbidity level was abnormal in 8 of 11 patients, averaging 8.2 units. The cephalin-flocculation test yielded a positive result in 4 of 11 patients. In only one patient was the serum bilirubin level elevated, and this to only 1.3 mg. per 100 cc. Hyperglobulinemia occurred in 13 of 14 patients, averaging 4.4 gm. per 100 cc. Minimal elevation of the alkaline phosphatase level was present in three. In seven patients the serum protein levels and/or flocculation tests were determined before and after treatment (Fig. 1).

The histologic changes in the four liver biopsy specimens included slight focal portal inflammation and swelling of the parenchymal cells, with occasional polynucleation and granular degeneration of the cytoplasm. A representative area is shown in Figure 2. In none were these changes considered evidence of significant hepatic disease.

COMMENT

In the 14 patients studied the only hepatic function tests which yielded significantly abnormal results were the cephalin flocculation and the thymol turbidity. Stillerman [3] and Maclagan [21] have previously reported abnormality of the flocculation tests in lymphogranuloma venereum. Jones and Rome,[25] however, found galactose tolerance, sulfobromophthalein excretion, urine urobilinogen, and serum bilirubin to be normal in 27 cases.

Similarly, the insignificant abnormality of dye excretion, alkaline phosphatase, bilirubin levels, and hepatic structure in the present study clearly shows that the abnormality of flocculations is not an indication of liver involvement. Such patterns are characteristic of hyperglobulinemic diseases * that do not produce hepatic damage.

The marked and constant hyperglobulinemia of lymphogranuloma venereum has been shown to represent largely elevation of the gamma globulin fraction.[24] It has been suggested that the lymphogranuloma venereum virus is particularly prone to stimulate the reticuloendothelial system, thus producing hyperglobulinemia.† Moreover, a wide group of chronic infections or related states are characterized by hyperglobulinemia, and in these instances elevation of gamma globulin has been considered to represent antibody production.‡

The data in the present study suggesting that the elevated levels of serum globulin and thymol turbidity are related to the activity of the disease are in agreement with other reports.§ As is shown in Figure 1, all but one of seven treated patients showed significant decrease of these levels to or toward normal. Failure of the globulin level or thymol turbidity to return to normal does not necessarily signify unsuccessful treatment. Return to a normal plasma protein pattern seems, however, reassuring evidence of adequate therapy.

As has been shown in other studies,|| apparent abnormality of hepatic function may not mean liver disease. Specific patterns of abnormality which are not seen in intrinsic hepatic disease do occur in hyperglobulinemic states.¶ When flocculation tests and globulin levels are markedly abnormal, but other functions are intact, it is well to consider hyperglobulinemic disease rather than primary liver disease as the probable cause. This seems particularly appropriate in lymphogranuloma venereum. Our studies showed no significant abnormality of the tests that measure parenchymal function nor of abnormalities of liver parenchyma on histological study. The flocculation-test abnormalities and hyperglobulinemia seemed parallel phenomena.

* References 2-4, 9, 13, 16, and 21.

† References 23, 24, and 29.

‡ References 15, 21, 24, and 43.

§ References 24-26 and 28.

|| References 1-13, 16, and 21.

¶ References 9-13.

SUMMARY

Fourteen patients with lymphogranuloma venereum were studied by means of the usual tests of hepatic function as well as liver biopsy in four cases. Thymol-turbidity and cephalin-flocculation tests were the only significantly abnormal ones. Hepatic structure, as seen in liver biopsy, was not significantly altered. The almost invariable hyperglobulinemia of lymphogranuloma venereum seems the most likely explanation for the abnormality of the above tests. A return of these tests, as well as the serum globulin levels, to or toward normal after therapy strongly suggests that treatment has been adequate.

Dr. B. Chomet, Chief, Laboratory Service, assisted in this study.

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Significance of Diphtheroids in Malignant Disease Studied by Germ-Free Techniques

Reevaluation in Hodgkin's Disease, Lymphoma, and Mouse Carcinoma

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A survey of an extensive literature on Hodgkin's disease shows it to contain many publications reporting implication of bacteria as the etiologic agent.* None of the work, however, has stood the test of time. Pertinent to our own study are the more recent reports concerning the isolation of acid-fast organisms [25] and of a "diphtheroid" [7] from the blood of patients with Hodgkin's disease, since, for a period of time, a diphtheroid with acid-fast properties was persistently isolated by us in blood cultures not only from patients with Hodgkin's disease but from patients with leukemia and lymphosarcoma as well and from both patients and mice with cancer.

It would serve no purpose to describe in detail the numerous experiments performed during four years in an attempt to determine whether these organisms really were carried in the blood stream of sufferers from Hodgkin's disease. The description and results of two major experiments will suffice to make clear the nature of the work which led up to the final one in which a germ-free technique, that of Dr. James A. Reyniers, University of Notre Dame, was employed.

EXPERIMENT 1.—*Tryptose Broth Cultures.*—As suggested by Fleisher,[7] 5 cc. samples of blood, drawn by routine methods of venipuncture, were cultured in McCartney bottles containing 15 cc. of tryptose broth (Difco). At intervals, 7 to 21 days after planting the original culture, 0.5 cc. samples of it were transferred to bottles of the same medium, and smears of the fluid were prepared and stained by Gram's method and Kinyoun's stain for acid-fast organisms. Wet preparations of each transfer were also studied under phase-contrast optics. Cultures and subcultures were plated onto trypticase-soy agar and trypticase-soy blood agar plates.

The cultures so treated were prepared from blood samples obtained from 31 patients with Hodgkin's disease or lymphosarcoma diagnosed by biopsy. All clinical stages of the disease were represented, ranging from recently-diagnosed, untreated cases to active cases of long duration subjected to many types of therapy. A total of 55 cultures (each involving 1 to 4 subcultures) were carried in the above medium.

In 20% of these cultures a "diphtheroid" was isolated. These organisms were never isolated from primary broth cultures but from agar plates. After approximately seven days the diphtheroids usually appeared in single or sparse colonies ranging in size from pinpoint to 10 to 15 mm. in diameter. All were of waxy consistency, were difficult to emulsify, and crackled sharply in the flame of a Bunsen burner.

The organisms appeared as coccoid bodies, rods, and club-shaped forms containing granular Gram-positive inclusions. In the rod form the inclusions were bipolar. The single consistent feature of the organism was the acid-fast staining property of its inclusions. Since attempts to separate the three forms were not successful, it became apparent that the variation in shape was a manifestation of pleomorphism. Comparison of the organisms isolated by us with those grown from three cultures supplied

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* References 8, 9, 15, 16, 21, and 22.

by Fleisher indicated that on the basis of morphology and staining characteristics (including acid-fastness) the bacteria were the same.

In order to check reproducibility of results, a second series of blood cultures, 53 in number, were taken from the same group of patients. This time only 10% of the cultures yielded the "diphtheroid" organism. The morphology and staining characteristics were identical to those just described.

EXPERIMENT 2. — *Pleuropneumonia-like Organism (PPLO) Medium.*—The inconsistent results obtained with tryptose broth in Experiment 1 led to a search for an enriched medium which would support growth of an apparently fastidious organism. Among the many media tested was that described by Morton and co-workers.[17]

This medium, used for the culture of pleuropneumonia-like organisms, contained 50 gm. of Bacto-beef heart, 10 gm. of Bacto-peptone, 5 gm. of sodium chloride, and 0.01 gm. of crystal violet per liter, to which, after adjustment to pH 7.8 and sterilization in the autoclave at 121 C for 15 minutes, 0.025 gm. of potassium tellurite was added aseptically. Just before use ascitic fluid (Difco) was added to the tubed medium in a final concentration of 25%. A 0.5 cc. sample of blood obtained by routine venipuncture was inoculated into 10 cc. of this medium and incubated at 37.5 C. After five days of incubation 0.5 cc. of the suspended culture was transferred to the same medium without crystal violet or tellurite. Three days later this subculture was streaked onto a trypticase-soy-blood agar plate which had been incubated for 48 hours. At each subculture smears were prepared and stained by Gram's method and Kinyoun's stain for acid-fast organisms.

Three series of cultures grown in this medium were studied. The first series consisted of cultures from 26 patients. From 24, or 92%, the acid-fast diphtheroid organism was again isolated, as in Experiment 1, from the blood agar plate.

The experiment was repeated on 47 lymphoma patients from whom 137 blood cultures were prepared. Technical manipulations were done in a sterile room under an ultraviolet light. This time there were 61 positive cultures, or 44%. Results fell into no pattern. Sporadic positive cultures grew from the blood of patients with Hodgkin's disease, lymphosarcoma, or leukemia; negative results were consistently obtained from one patient and consistently positive results from a few patients whose blood was cultured only a few times, but the great majority alternated between positive and negative.

A third series was run on blood from a group of tumor-bearing mice of the C3H strain. The same culture medium was used; the blood was obtained by the method of Kassel and Levitan.[14] Morphologically identical organisms were isolated from 4 of 13 cultures.

Details of sterilization are given in text. All seams and joints (including the attachment of the gloves) are sealed with Duco windshield cement. The tubing at the back of the hood is an inlet for air pressure used in generating the aerosol of peracetic acid during the second phase of sterilization of the interior. The pail contains sterilizing solution (Roccal-Chlorox), which covers the Stainless Steel tube leading into the hood (this forms the chemical trap). Tubes of sterile media inside of a sterile glove are placed in a weighted nylon stocking and attached to a Stainless steel chain, which emerges from the hood through the chemical trap. After immersion in the sterilizing solution for 10 minutes the material is drawn up into the hood. Excess sterilizing solution is removed from the outside of the glove by wiping with sterile gauze. The air filters, filled with glass wool, on the underside of the hood opposite the chemical trap, are not visible.

EXPERIMENT 3. — *Germ-Free Culture Methods.*—Although results obtained in Experiments 1 and 2 appeared to be compatible with those reported by Fleisher, we were still not satisfied that all sources of contamination had been ruled out. Use was therefore made of a small germ-free hood (Fig.) constructed by Dr. James A. Reyniers. His suggested techniques for sterilization had all been previously tested and proved at the Laboratories of Bacteriology, University of Notre Dame (Lobund Institute).

The hood is basically an air-tight box, with attached gloves, glass wool filters to permit the exchange of sterile air, and a chemical trap in which material can be both sterilized and introduced into the hood. Once sealed, the interior of the hood was sterilized by thorough washing with a mixture of 1% of a mixture containing 10% active alkyldimethylbenzylammonium chloride (Roccal) and sodium hypochlorite (Chlorox) 1:200. This was followed, after thorough drying of the air filters, by an aerosol spray of 1% peracetic acid. Subsequent ventilation, through the air filters, removed the acetic acid which remained after decomposition of the peracetic acid.

The sterility of the hood was tested by the exposure of tryptose broth and trypticase-soy-blood agar plates throughout the period of use. Chemical contamination of the medium (by Roccal-Chlorox mixture in the chemical trap) was controlled by carrying extra tubes of medium through the chemical bath and into the hood, opening the tubes, and subsequent to their removal planting an organism into them; their ability to support growth indicated a lack of chemical contamination.

Nonbiological material, such as test tubes, Petri dishes, syringes, needles, etc., to be introduced into the hood were first sterilized in containers by dry heat at 180 C for two hours. The containers were then placed in rubber gloves, and the unit was sterilized in an autoclave at 15 lb. pressure and 121 C for 45 minutes. The rubber gloves prevented contamination of the material by chemicals in the container when the unit was later introduced into the hood through the chemical-filled trap. Biological materials such as culture media were autoclaved in test tubes inside of rubber gloves. Ascitic fluid was introduced in ampules as prepared by Difco.

The technique for introducing the above materials into the hood was as follows: First the gloves were washed with the Roccal-Chlorox mixture to remove any dust, finger prints, etc., and then they were submerged in Roccal-Chlorox for 10 minutes prior to being taken into the hood through the trap. Blood samples were taken into the hood in vacutainer tubes after sterilization of the outside with Roccal-Chlorox for 10 minutes. The complete culture routine was carried on inside the hood, including primary cultures, subcultures, pouring of plates, and streaking of blood plates or slants.

Blood samples used in the cultures in the hood were obtained in the following manner: In the operating room the patient's antecubital fossa and adjacent areas were thoroughly scrubbed with pHisohex for 15 minutes. The patient was then draped with sterile towels and the antecubital fossa wiped dry with a sterile towel or allowed to air dry. One of the investigators, having scrubbed as for any operating room procedure and wearing sterile gown and gloves, withdrew 10 cc. of blood in a syringe previously coated with silicone and autoclaved with the needle attached. The sterile cellophane wrapper covering the sterile cap of a vacutainer tube (BD) was burned off over an alcohol lamp, and the blood was introduced into the tube. Each blood sample, the source of which was known only to one of the investigators (A. R.), was introduced into two vacutainer tubes, which were labeled in code. Four samples were taken at each bleeding, and duplicate sets of these tubes were sent to the culture room where, after careful cleaning with Roccal-Chlorox, one set was cultured in the germ-free hood, the other set cultured in the "sterile" room. The possibility of identifying duplicate tubes cultured in the two areas was limited by the system of coding.

Medium, amount of blood, time of subculture, and temperature of incubation were identical for each of the duplicate sets. The medium was controlled against chemical contamination, and tests of sterility inside the hood were carried on throughout the experiment.

A total of 30 persons were used in obtaining the blood samples. Nineteen were patients with Hodgkin's disease; five were presumably healthy controls; four were patients with leukemia; one was a patient with lymphosarcoma, and one was a patient with carcinoma of the lung.

During the course of the experiment 60 cultures were carried in the hood. A break in technique was discovered on the second run in the hood, when tryptose broth exposed in an open Petri dish became cloudy. An organism similar to B. subtilis and an Aspergillus were observed on three of the plates made during this culture. The hood was resterilized, and no further contamination was observed throughout the remainder of the experiment. Trypticase-soy-blood agar plates and tryptose broth exposed for 21 days in the hood showed no evidence of growth. Media used in the experiment were routinely tested for evidence of chemical contamination and were found to support bacterial growth in each instance.

Of the 60 cultures carried in the hood, 57 were negative on blood plates and/or blood slants after two weeks of incubation.

The duplicate samples used in the "sterile" room were carried in 48 cultures. Only four of these cultures were positive for the diphtheroid organism described above. Three of these cultures were from patients with Hodgkin's disease; one was from a patient with leukemia. Three isolated colonies of Staphylococcus were obtained in three cultures from Hodgkin's disease patients, and in one control culture Aspergillus was observed. Thus, of the total of 60 cultures carried in the germ-free hood, 3 contaminated cultures were observed during a period in which a break in technique had been discovered, but no cultures were positive for the "diphtheroid" organism previously described. The "contamination" rate in the sterile room appeared to be 8+% for the "diphtheroid" and 8+% for other organisms. In no instance were organisms observed in both cultures from the duplicate samples.

Results of Cultures

Culture Conditions	No. of Cultures	No. Positive for "Diphtheroids"	Per Cent Positive
1. Open laboratory, tryptose broth	55	11	20
2. Open laboratory, tryptose broth	53	5	10
3. Open laboratory, PPLO medium	26	24	92
4. Sterile room, PPLO medium	137	61	44
5. Sterile room, PPLO medium, blood drawn in operating room	48	4	8
6. Germ-free hood, PPLO medium, blood drawn in operating room	60	0	0
7. Sterile room, PPLO medium, blood from tumor-bearing mice	13	4	30
8. Germ-free hood, blood from tumor-bearing mice	8	0	0

During the operation of the germ-free hood, an additional group of C3H tumor-bearing mice were obtained. Blood from these animals was cultured in the hood under the same conditions as were the samples of human origin. In eight such cultures no organisms were isolated, in contrast to 30% positive results when the culture procedures were carried on outside the hood. The results may best be summarized in the accompanying Table.

COMMENT AND CONCLUSIONS

Several phases of the pathological picture in Hodgkin's disease are such as to have convinced many investigators that it is inflammatory in nature. The obvious approach, following such speculation, has been a long and unsuccessful search for a causative agent.

The early belief of Sternberg that the disease was a form of tuberculosis was revised when Reed [20] set it apart as a distinct disease entity. Next came Bunting and Yates,† who isolated a "diphtheroid," Corynebacterium hodgkini, from diseased nodes. After Cunningham [6] reported that this organism was a contaminant, no more was heard of a "diphtheroid" until 1952, when once again it was reported to have been isolated from the blood stream.[7] Our experience with this organism was that initially it was relatively easy to isolate, but as technical procedures became more stringent it appeared in our cultures less and less frequently. Finally, when the critical germ-free technique was adopted we failed completely to obtain growth, clearly indicating that the "diphtheroid" was a contaminant.

Though our experiments may not prove conclusively that Hodgkin's disease is not caused by an organism carried in the blood stream, they serve to emphasize the extremes to which an investigator must carry sterile techniques in order to rule out unusual contaminants. In our work meticulous attention to technique short of use of the germ-free hood served only to eliminate the commoner contaminants, leaving behind slower-growing more fastidious contaminating organisms of unknown origin and significance. The question of the origin of such an organism is always a critical one, particularly when one

† References 3-5.

is working with material from a disease of unknown etiology and questionable classification such as Hodgkin's. Minute details of every phase of the culture operation must be scrutinized for possible sources of contamination. Material considered acceptable for routine bacteriology almost invariably falls short of the requirements for germ-free work. For example, syringes used for routine venipuncture were found to leak air at both the joint with the needle and around the barrel; to eliminate this it was necessary to siliconize both barrel and the joint. With the plugging of each such loophole positivity decreases and results become more inconsistent. This can only indicate that the organism has not arisen from the specimen originally suspected as the source—an observation which should have significance for those who would implicate bacteria as the cause of cancer,‡ since it makes clear that techniques not indisputably germ-free are not acceptable in a field fraught with so many pitfalls.

As to the cause of Hodgkin's disease, the question of viral etiology remains still unsettled. The difficulties which have and will continue to beset workers in this particular field have been highlighted by Gordon, Grand, Bostick, and Moolton.§ The problem faced by others ‖ consists in proving the particulate matter, demonstrated by physical methods, to be living. Or, in the event a living agent—a virus—is isolated, to prove that it was obtained from the patient and not from the complex living systems employed to isolate it. Even when this is achieved, the imposing task of relating the agent to the disease will remain. However, the search must go on, for even "negative" results are affirmative in that they show up the investigational approaches which will prove unprofitable.

SUMMARY

A pleomorphic "diphtheroid," previously reported by others, was isolated from the blood of patients with Hodgkin's disease and lymphoma and from the blood of carcinomatous mice by routine culture methods. As the techniques became more stringent the percentage of positive cultures decreased, reaching the level of zero when the germ-free techniques of Dr. James A. Reyniers, of Notre Dame University, were utilized. The results clearly indicate that the organism came from some source other than the original blood sample and that rigorously sterile techniques must be used when dealing with the problem of organisms isolated from patients having a disease of unknown etiology.

‡ References 1, 11, 13, and 23-25.

§ References 2, 10, 12, and 18.

‖ References 2 and 19.

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Treatment in Internal Medicine

TREATMENT OF BACTERIAL PNEUMONIA

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MOST FORMS of bacterial pneumonia can be treated successfully at the present time. As a result, the mortality rate has declined from over 30% to less than 10% during the past two decades. However, deaths still occur frequently among small infants, in elderly persons, and in patients in whom treatment is not instituted early. Widespread use of antibiotics may have caused some reduction in the total incidence, but the number of cases of bacterial pneumonia has not declined in proportion to the striking decline in the mortality rate.[1] Viral infections of the respiratory tract and other inciting factors which predispose to pneumonia have not been controlled.

In most instances, treatment must be started before a precise bacteriological diagnosis is made. It is usually possible to conclude that the patient has a bacterial rather than a viral pneumonia because of the sudden onset, pleuritic pain, and rusty sputum. There is usually leucocytosis, although in alcoholics the white blood cell count is often normal or even low. Over 90% of bacterial pneumonias are caused by the Pneumococcus, and administration of therapy appropriate for this organism will therefore be adequate for most cases. However, since some of the more highly fatal forms of pneumonia are caused by other bacteria, it is important to attempt to establish a diagnosis when the patient is first seen. In addition to the clinical findings, examination of a Gram-stained smear of freshly obtained sputum is often a valuable aid in selection of the proper therapy. Of particular importance is the differentiation as to whether the predominant organism in the sputum is a Gram-positive coccus or a Gram-negative rod. Of the Gram-positive organisms, staphylococci are easily recognized but pneumococci and streptococci may be difficult to differentiate. Among the Gram-negatives, Klebsiella pneumoniae (Friedlander's bacillus) is easily identified by its large capsules. Other Gram-negative rods which may cause pneumonia are Hemophilus influenzae, Escherichia coli, and Pasteurella tularensis. Antibiotic therapy is instituted on the basis of the clinical picture and the information obtained from the direct sputum smear. Specimens for blood culture and sputum culture should always be obtained before drug therapy is started. The next day, when the results of these cultures are available, it is sometimes necessary to change the therapy.

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PNEUMOCOCCAL PNEUMONIA

The mechanism of recovery in pneumococcal pneumonia is such that a number of chemotherapeutic agents are equally effective in treatment of all but the severest cases. Because of their smooth capsules, pneumococci tend to resist phagocytosis in liquid media. Lung tissue, however, provides suitable surfaces against which leucocytes are able to trap and to ingest encapsulated pneumococci prior to the appearance of opsonizing antibody. This efficient defense mechanism, which is called "surface phagocytosis," operates in the absence of immune bodies and is responsible for destruction of pneumococci during the first few days of untreated pneumococcal infections.[2] Any antimicrobial agent which will aid this defense mechanism by inhibiting multiplication of the organisms, thereby preventing spread of the lesion, will assist the

host in controlling the infection. It is for this reason that agents with a relatively weak bacteriostatic action, such as the sulfonamides, often have a striking therapeutic effect in pneumococcal pneumonia.

Chemotherapy

Penicillin is unquestionably the most effective drug for the treatment of pneumococcal pneumonia, even though its superiority is difficult to demonstrate in the average case. In vitro, penicillin inhibits pneumococci in concentrations of 0.02 units per milliliter or less, its action is bactericidal, and resistant strains have not been encountered. For most cases, 600,000 units of procaine penicillin should be administered intramuscularly twice daily. After the patient is afebrile the dose may be decreased to 300,000 units once or twice daily. The total duration of therapy is usually five to seven days in the uncomplicated case; giving penicillin for a longer time does not hasten regression of the pulmonary infiltrations.

Some authorities prefer to administer aqueous solutions of crystalline penicillin rather than procaine penicillin routinely in the treatment of pneumococcal pneumonia.* Intramuscular doses of 10,000 to 100,000 units are given every three hours. This method, requiring more frequent injections, has few if any advantages. The higher peak concentrations produced in the blood and tissues are greatly in excess of those required to kill the Pneumococcus. To avoid such frequent injections, larger doses of aqueous penicillin, 300,000 to 1,000,0000 units, are sometimes administered every 8 or 12 hours.[4] This procedure takes advantage of the fact that after contact with the antibiotic has ceased a recovery period of several hours is required by pneumococci before they can resume multiplication.[5] Again, this plan offers no advantages over administration of procaine penicillin and merely floods the tissues with concentrations of antibiotic much larger than are needed for the maximal bactericidal action.

The above remarks apply to patients who are moderately ill on admission to the hospital and in whom treatment is instituted fairly early in the course of the disease. Patients who are desperately ill, on the other hand, should receive large doses of aqueous penicillin from the outset. Such cases occur particularly in elderly persons, in alcoholics, and in patients who do not seek medical attention early. With overwhelming infections time may be important, and the prompt establishment of high concentrations of the antibiotic in the tissues may be life saving. Furthermore, serious complications such as meningitis or endocarditis may be incipient, or already well established. One million units of crystalline penicillin should be given immediately by the intravenous route, to be followed by intramuscular injections of the same amount every two hours. If there is rapid improvement, and it becomes evident that endocarditis and meningitis are not present, frequent injections of crystalline penicillin can be discontinued and procaine penicillin can be started. An aggressive approach in this type of case may be an important factor in further reducing the mortality rate in pneumococcal infections. I have seen a number of seriously ill patients, treated with procaine penicillin, in whom signs of meningitis were absent on admission but appeared within two or three days. Similarly, acute endocarditis can be easily overlooked, and, as a result, patients who are receiving only procaine penicillin may be inadequately treated.

Although it is effective in milder cases, oral penicillin probably has little place in the treatment of pneumococcal pneumonia, since large doses must be given and absorption is quite irregular.[6] If the oral route is employed, at least 400,000 units should be given every six or eight hours, and the drug should be ingested at least an hour before or two hours after meals. Particularly in patients with severe infections, it is preferable to administer penicillin parenterally, where the pattern of absorption is much more constant.

* References 1 and 3.

Except in patients with overwhelming infections, the tetracycline antibiotics produce therapeutic results which are indistinguishable from those obtained with penicillin.† Tetracyclines are often administered empirically because of the possibility that the patient may be suffering from pneumonia due to a Gram-negative organism or possibly to a virus which will respond to these drugs. One to three grams should be administered orally each day in divided doses, depending on the severity of the illness. Intravenous preparations of tetracyclines are also available, and they should be administered in doses of 0.5 to 1.0 gm. every 12 hours to patients who cannot tolerate oral medications. Intramuscular preparations of tetracyclines may be adequate in milder cases, but because of the relatively low blood levels associated with their administration the intravenous forms are preferable for severe infections.‡ The chief disadvantages associated with use of the tetracyclines are the occurrence of gastrointestinal side-effects and the development of superinfections, which are most commonly caused by staphylococci. Such infections are a serious problem in many hospitals at the present time and are a potential danger in patients treated with tetracyclines or with penicillin.§

Erythromycin is also an excellent antibiotic for the treatment of pneumococcal pneumonia, and it gives results comparable to those obtained with penicillin in all except the severest cases.‖ Pneumococci are approximately 10 times as sensitive to erythromycin as to the tetracyclines, and blood levels obtained with erythromycin are roughly in the same range. Important advantages associated with the administration of erythromycin are the low incidence of side-effects and the infrequent occurrence of superinfections. Because of these advantages, erythromycin may often be selected as the antibiotic of choice in the treatment of pneumococcal pneumonia of mild or moderate severity. Dosages of the oral and parenteral forms are the same as for the tetracyclines.

Sulfonamides have been used successfully in the treatment of many patients with pneumococcal pneumonia. It has been clearly demonstrated, however, that the mortality rate is considerably higher with sulfonamides than with antibiotics in patients who have severe infection.[15] Sulfonamides cannot therefore be recommended except when antibiotics are not available.

Complications

In over 80% of patients who receive adequate treatment for pneumococcal pneumonia, signs of toxicity diminish rapidly and the temperature returns to below 100 F within 48 hours of starting therapy. Antibiotics are discontinued within a week, and physical and roentgenographic signs of pneumonia have cleared completely within three weeks. Of the complications which occur in the remainder, only those relating directly to the chest will be considered. Meningitis, endocarditis, otitis, arthritis, and pericarditis are beyond the scope of this review.

Prolonged Febrile Course.—In a small group of patients the temperature remains unaccountably elevated for longer than 48 hours. This occurs chiefly in alcoholics and other debilitated persons encountered in municipal institutions and is a familiar entity to those dealing with such patients. Every effort should be made to exclude the other complications discussed below. Despite the temperature elevations there is progressive clinical improvement, with a decrease in cough and sputum. The temperature declines slowly, and it is usually normal within 6 or 7 days, although elevations may occur for 10 or 12 days in some instances. The cause of the prolonged fever is unknown. Small undetectable pleural effusions, empyemas, or areas of atelectasis may be responsible, but this has not been proved. There is a tendency among those unfamiliar with this problem to change antibiotics empirically every two or three days. Unless there is

† References 7 and 8.

‡ Spies, H. W.; Lepper, M. H., and Dowling, H. F.: Use of Tetracycline Hydrochloride Intramuscularly, in Reference 9, p. 619. Reference 10.

§ References 11 and 12.

‖ References 13 and 14.

clear-cut clinical or bacteriological indication for such a change, it is preferable to continue the original therapy until the temperature has been normal for 48 hours.

Pleural Effusion.—This is probably the commonest cause of persistent fever in patients who are otherwise showing clinical improvement, i. e., decrease in toxicity, cough, and sputum. The presence of fluid is usually detected by physical signs or x-ray examination between the third and sixth days after therapy is started, but it occasionally appears later, during convalesence. Interlobar collections may be difficult to recognize and to aspirate. The fluid is usually thin and yellow and is sterile. The temperature may remain elevated for 10 to 14 days in such cases. Small amounts of fluid are reabsorbed in a week or two and do not need to be aspirated. With large amounts, repeated thoracenteses are indicated in an attempt to reexpand the lung as completely as possible. The fluid may thicken after a time and become loculated. Enzymatic débridement should then be attempted, and this is often helpful in thinning the exudate and freeing the loculations. Decortication may be indicated in a small percentage of cases, but the pleural exudate is usually absorbed to a remarkable degree over a period of weeks or months.

Empyema.—A rare complication nowadays, empyema is usually encountered in patients treated late in the course of the disease and is present at the time of admission to the hospital. The patient is usually very ill, with a positive blood culture, and should receive intensive penicillin therapy for the underlying disease. When the empyema fluid is examined microscopically and by culture, the presence of pneumococci is readily demonstrated.

In early acute empyemas, when the fluid may be heavily infected but has not become thick and creamy, intermittent aspiration and instillation of antibiotics will usually eradicate the infection. The empyema fluid is removed as completely as possible, and penicillin, 100,000 to 250,000 units dissolved in 5 or 10 ml. of isotonic saline solution, is injected into the pleural space. The fluid should be aspirated every day or two, and if it is very thick the empyema cavity should be irrigated with 200 cc. of sterile saline solution before the antibiotic is instilled. Empyemas which respond to needle aspiration usually do so within 7 to 14 days. In many cases, particularly when the fluid is very thick at the outset, the pus becomes sterilized but persists and becomes loculated. Thick exudate and fibrin clots tend to block the aspirating needle, making it impossible to remove the fluid completely. The judicious intrapleural injection of fibrinolytic enzymes, either a combination of streptokinase and streptodornase or crystalline trypsin, is then indicated. With this enzymatic débridement fibrin clots are dissolved, pus is liquified, and loculations are broken down. Although favorable results are reported, many physicians have been disappointed with the technique of injecting enzymes into the pleural space. Details of timing and dosage are undoubtedly important in determining success or failure, and articles written by those experienced with this technique should be consulted.¶ Surgical drainage is indicated if the empyema cavity has not been obliterated after three or four weeks.

Superinfections.—This complication usually occurs after five or six days of therapy, and its presence should be suspected when, after initial improvement, the temperature again becomes elevated, cough becomes more frequent, and there is an increase in sputum production. Physical signs of pneumonia reappear, and x-rays often show a spread of the pulmonary infiltrations. Superinfections are usually caused by antibiotic-resistant staphylococci or by Gram-negative rods. Blood cultures should be repeated, and careful smears and cultures of the sputum should be made. If there is evidence that the Pneumococcus has been replaced by a nearly pure culture of another pathogen, antibiotic therapy should be changed on the basis of the

¶ References 16 and 17.

sensitivity of the newly discovered organism to various antibiotics. Specific therapy for the organisms most likely to cause superinfections will be considered in subsequent sections.

Delayed Resolution.—Delay beyond three weeks in clearing of physical and x-ray signs of consolidation occurs most commonly in alcoholics and in elderly or debilitated persons. It is probable that some nutritional deficiency is associated with impairment of healing, but the exact mechanism has not been elucidated. In the patients with slowly resolving bacterial pneumonias, healing eventually occurs with scarring, fibrosis, and partial collapse of the involved lobe. Aside from a program aimed at improving the patient's general nutritional status, there is no specific management. Aerosols containing antibiotics, proteolytic enzymes, and bronchodilators have not been particularly helpful, although these measures seem to bring about improvement in some cases. The possibility of an underlying neoplasm must always be kept in mind when a pneumonia does not clear promptly. Sputum cytology, tomograms, and bronchoscopy are helpful in excluding the presence of a tumor; if the results are equivocal, thoracotomy should be performed.

Relapse.—With inadequate dosage, or when antibiotics are given for less than five to seven days, relapse of the pneumonia may occur. Differentiation between a relapse and a superinfection may be difficult, but it can usually be accomplished by careful bacteriological studies of the sputum. With adequate treatment relapse is rare, and the appearance of a second pneumonia within a few weeks usually represents a reinfection with a new organism. The clinical manifestations are similar to those observed during the initial attack, and a complete diagnostic work-up should be carried out, just as on the first occasion. When two attacks of pneumococcal pneumonia occur in a single lobe within a few weeks, the possibility of a tumor or of some structural defect should be considered. It should be kept in mind, however, that second attacks do occur without any underlying abnormality.

STREPTOCOCCAL PNEUMONIA

With the decline in streptococcal infections in general, this form of pneumonia is rare at the present time. Most cases are secondary to viral infections such as influenza or measles or follow a streptococcal sore throat. The presence of pneumonia may be obscured by the associated illness, thereby causing a delay in starting therapy. The frequent occurrence in respiratory secretions of beta-hemolytic streptococci complicates bacteriological studies, but the presence of large numbers of these organisms in cultures of freshly obtained sputum makes the diagnosis quite certain. Blood cultures are infrequently positive. The treatment of pneumonia caused by Group A streptococci is the same as that described for pneumococcal pneumonia. Pleural involvement is common. The fluid is often sterile and can be managed by repeated aspirations. When infected, the pleural fluid tends to be thin and hemorrhagic, and the intrapleural installation of penicillin is an important part of the therapy.

Enterococci, which not infrequently cause beta hemolysis, are sometimes cultured from the sputum of patients with pneumonia. Although rarely a primary cause of pulmonary infections, these Group D streptococci are probably responsible for an increasing number of superinfections. Enterococci are relatively insensitive to penicillin alone, and treatment should consist of a combination of penicillin and streptomycin. Viridans streptococci may on rare occasions cause pneumonia. Diagnosis is virtually impossible unless the organism can be cultured from the blood or pleural fluid. Most members of the viridans group are penicillin-sensitive.

STAPHYLOCOCCAL PNEUMONIA

Staphylococcal pneumonias have in the past been rare except in association with epidemics of measles or influenza. At present, an increasing number of cases is being

encountered in which the infection is hospital-acquired and is caused by antibiotic-resistant staphylococci.# Such pneumonias occur commonly in patients who are receiving antibiotics, chiefly penicillin or one of the tetracyclines, either for treatment or for prophylaxis. Suppression of the susceptible bacterial flora allows pathogenic staphylococci, which are widespread in the hospital environment and are resistant to antibiotics the patient is receiving, to invade the host's tissues. In patients with staphylococcal infections elsewhere in the body, the organisms may reach the lungs through the blood stream. Tissue necrosis, with the formation of multiple lung abscesses, is a characteristic feature of staphylococcal pneumonia and contributes to the serious nature of the infection. Diagnosis may be difficult, but it can usually be established by obtaining a relatively pure culture of staphylococci in the sputum, particularly when this is present in several successive specimens. Blood cultures are positive in a high percentage of the severer cases and often help to establish the diagnosis when the results of sputum cultures are doubtful.

Fifty to seventy-five per cent of staphylococci isolated from hospitalized patients are resistant to penicillin, streptomycin, and the tetracyclines.[20] Less than 10% are resistant to erythromycin, chloramphenicol and bacitracin. The pattern varies widely from case to case, however, and therefore determination of the sensitivity of the infecting organism to various antibiotics is important in management of the individual patient. Staphylococci are usually either very sensitive or quite resistant to a given antibiotic, and the pertinent information can be quickly and reliably obtained with the disc method of sensitivity testing.

It is usually necessary to start treatment before results of antibiotic sensitivity tests are available, and the antibiotics most likely to be effective should be selected. This varies from hospital to hospital, but the following recommendations will apply to most. Penicillin may be started, in the doses indicated below, but should not be the only antibiotic given if it is likely that the organism is penicillin-resistant. Erthyromycin or chloramphenicol, or preferably both, should be administered in doses of 2 to 4 gm. daily. Advantages of giving both are a probable enhancement of the therapeutic effect and a delay in the emergence of organisms resistant to either antibiotic. Seriously ill patients, with positive blood cultures, should also receive bacitracin intramuscularly in doses of 15,000 to 25,000 units every six hours. This antibiotic should be used cautiously, since it causes renal damage in some patients, but nephrotoxicity is rarely a problem if renal function is good when treatment is started. A routine urinalysis and blood urea nitrogen determination should be obtained at least twice weekly in patients receiving bacitracin. Slight proteinuria and an increase in red blood cells in the urinary sediment indicate renal irritation, but these changes subside promptly when the drug is discontinued. If possible, it is advisable to administer bacitracin for no longer than seven days and to allow an interval of four or five days before a second course is started. However, I have recently seen patients, seriously ill with staphylococcal infections, who received bacitracin continuously for longer than a month without evidence of damage to the kidneys.

If the infecting Staphylococcus is penicillin-sensitive, this antibiotic should of course be given in large doses. For severe infections, 1,000,000 or 2,000,000 units of aqueous penicillin should be injected intramuscularly every two hours. An alternative plan is to administer 10,000,000 to 25,000,000 units daily as a continuous intravenous infusion. With either route, probenecid in oral doses of 0.5 gm. every six hours should also be given to further enhance the blood levels of penicillin. Procaine penicillin, 600,000 units every eight hours intramuscularly, provides adequate therapy later in the course of the illness. Even with penicillin-resistant organisms, there is evidence indicating that penicillin may be effective when given in large

References 18 and 19.

doses in conjunction with other antibiotics. Penicillin-resistant staphylococci are penicillinase-producers, but they may be susceptible to the action of penicillin if the effect of this penicillin-destroying enzyme can be overcome. Furthermore, infections caused by penicillin-resistant staphylococci have been found by some observers to respond most favorably to regimens in which penicillin was included.[21] This is a subject which deserves further study.

The response to antibiotic therapy in patients with staphylococcal pneumonia occurs much more slowly than in those with pneumococcal or streptococcal pneumonias. The temperature declines slowly over a period of two or three weeks and the patient usually appears very ill and toxic for a week or more. Cortisone or corticotropin may be indicated in certain patients with profound manifestations of toxicity. These hormones should be given only after effective antibiotic therapy is under way, and they should be discontinued if possible within five to seven days. Controlled clinical data are not available, and the possible good and bad effects of steroid therapy need to be evaluated in each individual case. One aspect of therapy about which there is no controversey is the importance of finding and draining all suppurative foci as soon as possible. Pleural complications are common and are treated according to the principles outlined in the section on pneumococcal pneumonia. Antibiotics should be continued for several days after the temperature returns to normal. The total duration of therapy is rarely less than three weeks. Because of their severe, fulminating nature, and the tendency to develop metastatic foci throughout the body, the mortality rate in staphylococcal pneumonias remains high. Over-all figures are difficult to obtain, but in patients who are bacteremic 25% to 50% fail to survive. *

KLEBSIELLA (FRIEDLÄNDER) PNEUMONIA

This serious form of pneumonia occurs mostly in persons over 40 years of age who are chronic alcoholics or who have some other debilitating disease. Despite the susceptibility of K. pneumoniae to a number of antibiotics, the mortality rate remains over 50% because of the fulminating character of the infection and the fact that many patients are not treated until late in the course of the disease.[22] The sputum is characteristically brick-red, sticky, and gelatinous, and stained smears reveal large numbers of Gram-negative bacilli with large capsules. Cultures reveal a heavy growth of shiny, mucoid colonies. X-rays show massive consolidation of the involved lobes. Tissue necrosis occures rapidly, leading to abscess formation.

Therapy should be started immediately with one of the tetracyclines or chloramphenicol, in doses of 3 or 4 gm. daily. In patients too ill to take oral medications, one of these antibiotics should be given intravenously in doses of 0.5 to 1 gm. every 8 to 12 hours. Streptomycin should also be given in doses of 2 to 4 gm. daily (0.5 to 1 gm. intramuscularly every six hours). Sulfonamides have been used extensively in the past, but they probably add little to the therapy when antibiotics are given in adequate dosage. Empyema is common; streptomycin should be injected intrapleurally in doses of 50 to 100 mg. in conjunction with frequent aspiration and irrigation of the empyema fluid.

Patients with Klebsiella pneumonia are usually very ill and respond to treatment slowly. As with staphylococcal pneumonias, antibiotics must usually be continued for at least three weeks. In the patients who survive, residual abscesses, bronchiectasis, and pulmonary fibrosis are common. When these are confined to a lobe or pulmonary segment, excisional surgery should be considered.

PNEUMONIA DUE TO OTHER GRAM-NEGATIVE BACILLI

Not infrequently in children, and occasionally in adults, H. influenzae is the cause of pneumonia. Children should receive chloramphenicol or a tetracycline, 50 to 100 mg. per

* References 18 and 20.

kilogram of body weight per day; 2 to 4 gm. is the usual daily dose for adults. In severe infections, streptomycin should be given in addition.

P. tularensis is rarely a primary cause of pneumonia, and the secondary form can usually be diagnosed by an adequate history and by the presence of lesions of tularemia elsewhere in the body. Treatment is the same as for Klebsiella pneumonia.

Certain of the enteric Gram-negative bacilli, chiefly the coliforms, Pseudomonas, and Proteus, are increasingly important as a cause of superinfections and frequently involve the lungs.[12] Treatment of pneumonia due to coliform bacteria is the same as for Klebsiella pneumonia. However, sensitivity tests should be performed, since many of these organisms are now resistant to various antibiotics. Proteus infections are difficult to treat but are most likely to respond to sulfonamides, streptomycin, tetracyclines, or chloramphenicol. One group has reported impressive results in bacteremic patients treated with a combination of oxytetracycline and dihydrostreptomycin.[28] Patients with systemic infections due to Pseudomonas aeruginosa should receive polymyxin B intramuscularly in doses of 50 mg. every 8 to 12 hours. Because of its nephrotoxicity, neurotoxicity, and pain at the sight of injection, this antibiotic should be used with caution and only after a specific bacteriological diagnosis has been made. A tetracycline should be administered in addition to polymyxin, since the two appear to have a synergistic action against Pseudomonas.† In general, infections with these enteric bacilli respond poorly to therapy, and the mortality rate is high.

SUMMARY

Despite a marked decline in the mortality rate, bacterial pneumonia remains a common and serious problem. This review has emphasized the importance of an early accurate bacteriological diagnosis and prompt administration of the proper chemotherapeutic agents. Superinfections are of growing importance both with Gram-positive and with Gram-negative bacteria, and accurately performed antibiotic sensitivity tests are a valuable aid in guiding therapy.

† Canarile, L.; Osborne, W.; Johnston, S., and Bunn, P.: A Pattern for the in Vitro and in Vivo Control of Pseudomonas Aeruginosa, Reference 9, p. 210.

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Case Reports

CHRONIC RENAL DISEASE WITH SECONDARY HYPERPARATHYROIDISM

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A WELL-DOCUMENTED case of renal disease in an adult with marked secondary hyperparathyroidism and metastatic calcinosis is of sufficient rarity and interest to warrant publication.

A distinction between primary and secondary hyperparathyroidism is not always simple, for primary hyperparathyroidism in late phases of the disease may effect the renal function to such an extent as to reverse its originally characteristic calcium-phosphorus balance. In primary hyperparathyroidism one expects low serum inorganic phosphorus and high serum calcium and phosphatase levels with increased output of calcium in the urine, whereas in hyperparathyroidism secondary to chronic renal insufficiency with nitrogen retention phosphate is retained by the kidney, the serum inorganic phosphorus level is elevated, and the calcium level is low. If in the course of longstanding primary hyperparathyroidism renal calcinosis or lithiasis becomes sufficiently severe to interfere with renal function, the originally low phosphorus blood level may eventually rise, the calcium level fall, and the changes in blood chemistry may approach the pattern of secondary hyperplasia.

The major problem in this case concerned the decision as to whether the disturbed calcium-phosphorus metabolism, the demineralization of the skeleton system and the renal insufficiency resulted from an adenoma of a parathyroid gland or whether primary renal insufficiency initiated the chain of events causing secondary hyperplasia of parathyroid glands. A dissection of the neck in search for enlarged parathyroid gland would have been indicated only if the diagnosis of primary hyperparathyroidism could have been established.

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REPORT OF CASE

A 45-year-old white woman was admitted to the hospital on Sept. 6, 1954, because of pallor, weakness, dyspnea on exertion, and tender subcutaneous nodules over the arms and legs.

Her present illness began in December, 1953, with pain and soreness in the posterior part of the chest radiating anteriorly into the arms, hips, and legs. The soreness was noted particularly in the joints, which would swell but did not become red. She also had some epigastric discomfort at this time and was instructed by her local physician to drink large quantities of milk. Her condition was unchanged for a few months until February, 1954, when she noted some tender nodules beneath her skin. Her joint pain became less; however, she noted increasing pallor and weakness with dyspnea on exertion. Hospitalization was advised at this time but was declined by the patient, and she was treated at home with hematinics of all kinds, which failed to correct her anemia. She continued to be weak and began having considerable nausea with vomiting until, by the time of hospital admission, she had lost 50 lb.

The past history and family history were not contributory. She had one living child and three spontaneous abortions, the cause for which was unknown. Systemic review was negative. She had no complaints referable to the urinary tract.

On physical examination she appeared a very pale well-developed middle-aged woman. Eye grounds were normal. Mucous membranes of the mouth and tongue showed no redness or atrophy. Palpation of the neck did not reveal abnormalities. Lungs were clear and resonant. Blood pressure was 126/70, with an apex beat in the sixth interspace 7 to 8 cm. from the midsternal line. There was a rough systolic and short diastolic murmur over the precordial area, loudest in the fourth left interspace at the sternal border and transmitted toward the apex. No thrills or friction rubs were noted. The abdomen and external genitalia were normal. The internal genitalia had been removed. Over the

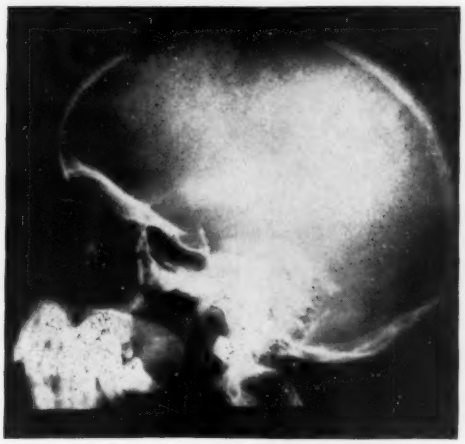
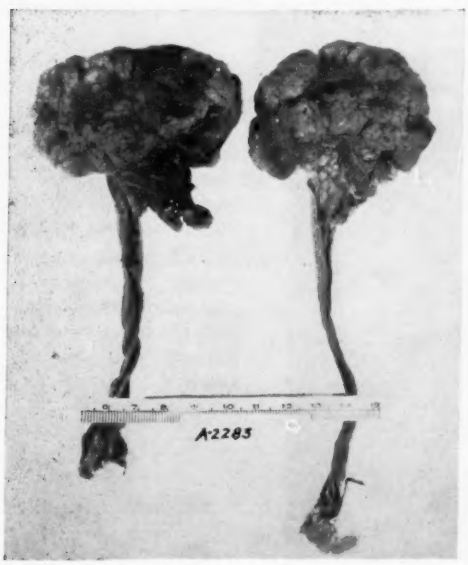


Fig. 1.—X-ray of skull, showing "ground glass" appearance.

extremities there were numerous discrete tender nodules, most prominent in the lower extremities, arranged in a chain-like fashion. They ranged from about the size of a pea up to about 2×5 cm. The larger nodules appeared to be formed by coalescence of the smaller ones.

Urinalysis showed many pus cells, 1+ sugar, 4+ albumin, acid reaction, and specific gravity of 1.010. Hemoglobin was 4.4 gm. RBC were 1,500,000; WBC, 11,100, with a normal differential count. Sedimentation rate was 55 mm. in 15 minutes, 78 mm. in 30 minutes, 80 mm. in 45 minutes, 81 mm. in one hour (Wintrobe and Lundsberg's method), with a correction factor of 19. NPN was 122 mg. per 100 cc.; bilirubin was 0.55 mg. per 100 cc. Calcium was 8.8 mg. per 100 cc.; inorganic phosphorus was 11.15 mg. per 100 cc. Alkaline phosphatase was 13.8 Bodansky units. Sulkowitch test of the urine was negative. Serum protein was 6.8 gm. per 100 cc., with albumin 4.1 gm. and globulin 2.7 gm. per 100 cc. CO_2-combining power was 20 vol. %. The red cell fragility was normal. Gastric analysis showed the presence of free hydrochloric acid, and sternal marrow aspirate showed normoblastic hyperplasia. X-ray examination of the pelvis, chest, and skull showed slight to moderate demineralization. In the bones of the cranium this was manifest as small punctate areas of decreased density, which produced a ground-glass appearance. An intravenous pyelogram showed only minimal excretion of the dye bilaterally after 30 minutes. There were no shadows consistent with urinary calculi. All of the arteries except the aorta showed marked calcification of their walls. A biopsy of one of the subcutaneous nodules showed focal calcification in the subcutaneous fat tissue.

Fig. 2.—Gross photograph of the contracted kidneys, showing pyelonephritic scarring.



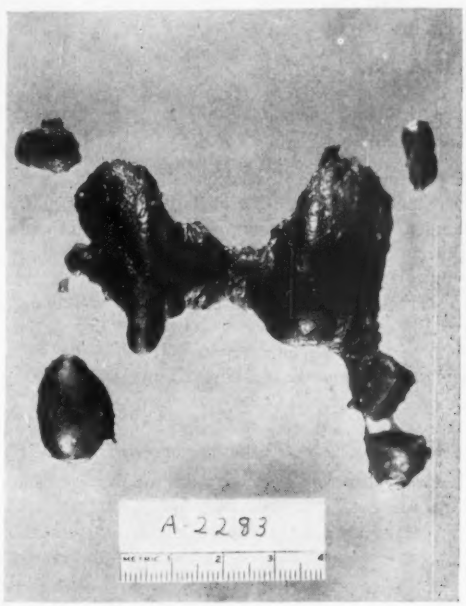


Fig. 3.—Gross photograph of thyroid and four enlarged parathyroid glands.

The patient's condition remained essentially unchanged during her period of hospitalization. The anemia proved refractory to all treatment except blood transfusions. She ran a low-grade fever, oral temperature ranging from 99.3 to 100.3 F. She was given 98 gm. of sodium citrate and 140 gm. of citric acid daily. This was dissolved in water

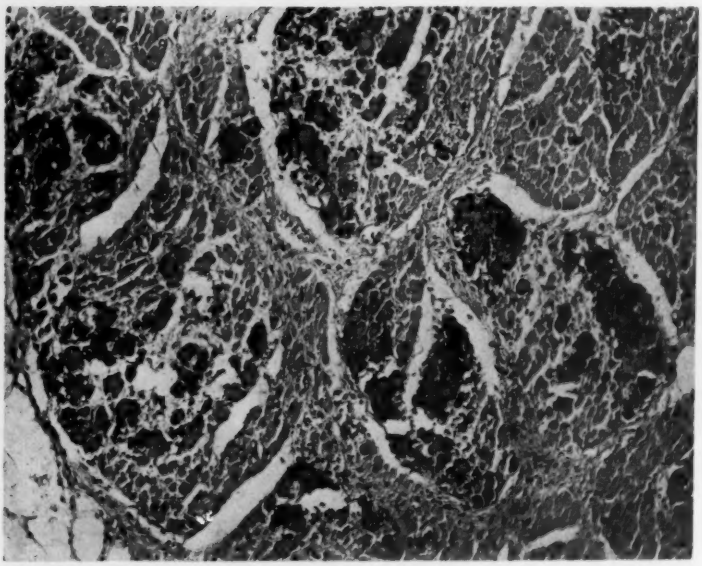


Fig. 4.—Low-power photomicrograph of heart, showing calcification of many myocardial fibers.

and given orally in divided doses. Milk and cheese were eliminated from her diet; vitamin D, 50,000 units a day, and calcium in the form of calcium gluconate were given. CO_2-combining power three weeks later was 30 vol. % and continued to rise to 48 vol. %. The NPN remained over 120 mg. per 100 cc., and the urine findings were unchanged, with persistent albuminuria, many white blood cells, and a fixed specific gravity. Eventually her condition deteriorated, with increasing drowsiness, nausea, vomiting, and headache. She died Dec. 9, 1954, about one year after the onset of symptoms.

Autopsy Findings.—Scattered throughout the subcutaneous tissue were gritty, firm nodules 2 to 4 mm. in diameter. Microscopically they showed foci of calcification and fat necrosis.

The heart was moderately enlarged, weighing 480 gm., with left ventricular predominance. The pericardium was covered with fibrinous exudate. Throughout the myocardium of the left atrium and ventricle, parallel to the muscle bundles, were conspicuous streaks of gritty yellowish material. At the base of the left side of the heart large subendothelial deposits of similar hard calcific material produced nodular projections which extended to involve and immobilize the aortic and mitral valves. The pulmonic and tricuspid valves were not involved nor was the endocardium of the right

Fig. 5.—High-power photomicrograph of heart, showing focal necrosis and inflammatory infiltrate. Arrows indicate fragments of necrotic muscle.

atrium or ventricle. Associated with the calcific deposits in the heart were definite microscopic degenerative changes in myocardial fibers, with loss of striations and focal necrosis with mononuclear-cell inflammatory reaction. Occasionally such foci of degeneration were found without evidence of calcification.

The lungs showed mild edema and no evidence of calcification. The aorta showed only mild arteriosclerosis.

The kidneys were contracted, weighing 46 and 47 gm. Their surfaces showed large, flat, depressed scars of irregular outline occupying most of each kidney. The intervening parenchyma was coarsely granular. The urinary tract was free of stones. Histologically, the kidney showed typical pyelonephritic contraction, with extensive loss of glomeruli, fibrosis, and dilatation of tubules filled with colloid-like casts. This, coupled with the thin tubular epithelium gave a thyroid-like appearance. In focal areas calcium deposits were found in tubular lumina, tubular epithelial cells, adjacent basement membranes, and connective tissue.

The stomach and intestinal tract were free of calcium deposits. The thyroid gland was normal.

The four parathyroid glands were diffusely enlarged, with the following weights: right lower, 1.5 gm.; left lower, 1.6 gm.; right upper, 0.3 gm.; left upper, 0.4 gm. The left lower gland was surrounded by a thin calcified shell, and the interior was pale gray, in contrast to the darker brown color of the others. The normal fat tissue of the parathyroid glands was reduced to tiny foci widely separated by sheets and strands of epithelial cells. Occasionally the cells were in acinar arrangement. Both chief cells and oxyphile cells were numerous, and in the right lower gland was a large discrete nodule of oxyphiles. In this nodule the nuclei tended to be darker and larger and varied somewhat in shape and size. The left lower gland was surrounded by thick calcified capsule. Most of the parenchyma was replaced by moderately cellular loose connective tissue, which occupied large areas in the section and extended between the few remaining clusters of epithelial cells, separating them into islands.

Sections of bone showed "moth-eaten" foci of resorption of trabeculae lined by osteoclasts and replacement of the marrow by fibrous tissue. In other areas osteoblasts were well developed and narrow osteoid seams were found. The over-all effect was that of patchy rarefaction.

COMMENT

The deposition of calcium-phosphorus salts in tissue is described as depending on the product of calcium and phosphorus values in the serum. In the adult this product is considered normal when in the range of 30-40 mg., a value which apparently permits normal calcification of newly formed bone. In primary hyperparathyroidism, when the serum phosphorus level falls, calcium is mobilized from the bone and its serum level rises, the product usually remaining about normal. In chronic renal insufficiency, when phosphorus is retained and the serum level rises, the calcium level tends to fall slightly and the calcium-phosphorus product may reach very high values. The mechanism of this complicated homeostatic process is poorly understood. It is postulated that a low serum calcium level caused by phosphate retention stimulates the parathyroid gland, mobilizing calcium from the skeletal system. In the presence of phosphate retention the calcium-phosphorus product may exeed 60 or 70 mg., and calcium phosphate may precipitate in many organs, particularly in the walls of medium-sized arteries and in the skin and subcutaneous tissues. Of the parenchymatous organs, kidney, lung, and stomach are frequent sites of deposition of metastatic calcinosis.

When these findings associated with phosphate retention occur in primary hyperparathyroidism, it is caused by complicating renal failure, which sometimes appears late in the course of the disease. The kidney damage in these cases is caused by either nephrocalcinosis or nephrolithiasis, which eventually may produce renal failure, nitrogen retention, and an elevated serum inorganic phosphorus. In the case reported here there were neither kidney stones nor extensive nephrocalcinosis to explain the renal disease. The renal failure, therefore, must have been due to other causes, such as chronic pyelonephritis or chronic glomerulonephritis, with the calcium-phosphorus disturbance a secondary phenomenon. The finding of normal blood pressure, the lack of previous history of glomerulonephritis, and the absence of hematuria made pyelonephritis the more likely diagnosis.

Therapy could only be palliative, since the underlying renal disease was advanced and irreversible. The aim was to correct the

acidosis, to supply in the diet additional calcium, and to restrict the intake of phosphate. Vitamin D and citric acid were added to enhance the gastrointestinal absorption of calcium. Milk, which is very high in phosphate, was deleted from the diet. It is interesting to note that the foci of metastatic calcification in this case first became evident shortly after the patient started drinking large amounts of milk for her "arthritis."

The autopsy findings confirmed the clinical diagnosis. The kidney changes were those of advanced pyelonephritis contraction, and the four enlarged parathyroid glands showed features of severe secondary hyperplasia. The bone changes reflected the hyperparathyroidism, showing marked patchy osteoclastic resorption and active osteoblastic formation of new bone. In the usual case of primary hyperparathyroidism much of the newly formed bone matrix remains uncalcified, perhaps because it is laid down so rapidly. In the case presented here the newformed bone evidently was promptly calcified, since only narrow seams of osteoid could be found. This is not surprising when one considers that the product of the values for serum calcium and inorganic phosphorus was about 100 mg. (calcium, 8.8 mg.; phosphorus, 11.15 mg.).

The finding of focal necrosis and severe calcinosis in the heart was an interesting feature. It was possible to find small foci of necrosis in the myocardium in areas free of detectable calcium (von Kossa stain). This finding suggests strongly that focal myocardial necroses preceded the calcium deposition and that this sequence explains the unusual severity of the calcification in the myocardium. Among 13 cases of dystrophic calcification of the myocardium reported by Gore and Arons, 12 cases had azotemia but a definite pathogenetic factor could not be established. In the case presented here we can offer no adequate explanation for the focal areas of myocardial necrosis.

SUMMARY

A case of severe secondary parathyroid hyperplasia is presented, and the differentiation from primary hyperparathyroidism is discussed.

The clinical diagnosis, including that of primary pyelonephritic contraction, was confirmed by autopsy.

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REVERSAL OF RENAL INSUFFICIENCY IN GOUT

Report of a Case Treated with Probenecid (Benemid)

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RECOGNITION and treatment of reversible disease is the primary function of the physician. This is particularly true when pathological processes involve a vital organ, such as the kidney, where progression of the lesions may lead to functional insufficiency and death. It is the purpose of this paper to review the problem of the renal complications of disturbed uric acid metabolism in gout and to present a case of severe primary gout in a young man with renal insufficiency in whom return to normal renal function occurred during treatment with probenecid (Benemid) over a 34-month period. During this time marked decrease in urate deposits elsewhere besides the kidney occurred, such as visible tophi, and improvement in the state of the clinical gouty arthritis also was seen. It is felt that the observation of the improvement in the renal function of this patient aids in clarifying the pathogenesis of the renal failure in gout and indicates that changes in the gouty kidney may be reversible in a relatively early stage of the pathological process.

A 31-year-old white man was seen for the first time in October, 1951, when he was hospitalized for an acute attack of gout. There is no known family history of gout, but the patient does not know many of his relatives. His episodes of joint pain began eight years previously, at the age of 23 years. At first only the great toe and the knees were involved. The number of attacks per year gradually increased, as did the number of joints involved. For the last year prior to admission the patient was not symptom-free between the acute joint flare-ups, having enough interval joint discomfort which prevented his working. He had lost 30 lb. and had passed a number of uric acid stones in the urine. The episode precipitating his admission began six weeks prior to entry with a fever of 103 F and marked pain in the shoulders, elbows, wrists, fingers, knees, and ankles. He took acetylsalcylic acid and colchicine, without sustained relief, the exact dosage not being clear.

Examination.—The patient was well developed but emaciated, weighing 98 lb. He was in severe joint discomfort, unable to get out of the wheel chair which brought him to the ward. When he was lifted bodily from the chair onto a bed, he burst into tears because of the intense pain of this movement. Large ulcerating tophi (Fig. 1) were present. There were painful warm tender joints of the feet, ankles, knees, elbows, and fingers. Enlarged bursae filled with urates were noted over the elbows and knees. The blood pressure was 120/70. The rest of the examination was not remarkable.

Laboratory Data.—Blood cell count, serology, and serum cholesterol were normal. BUN, 15 mg. per 100 cc. Urine showed a specific gravity of 1.008, a trace of albumin, and 30 to 40 WBC in the sediment. PSP excretion (Fig. 3) showed 15% in the first 15 minutes and a total of 66% in 2 hours. A Fishberg concentration test revealed a maximum specific gravity of 1.010. The serum uric acid was 11.5 mg. per 100 cc.

X-Rays.—Film of the chest was normal. An intravenous pyelogram showed poor dye excretion. Retrograde pyelography showed slight clubbing of the middle group of calyces on the left, suggesting pyelonephritis. Films of the joints of the hands revealed punched-out areas consistent with gout.

Course.—Urate crystals were demonstrated in material removed from a tophus. The patient was given colchicine 0.5 mg. every 2 hours, and within 24 hours marked symptomatic relief was obtained. He was then continued on colchicine 0.5 mg. twice daily. Prior to discharge he received chloramphenicol for four days because of the urinary tract infection. Antibiotics were not administered at any other time to this patient. He was discharged on maintenance colchicine and a low-purine diet.

The patient was next seen one year later, in 1952. In the interim he had been mildly improved on the program noted but was still unable to work because of joint discomfort. He was readmitted with a flare-up in arthritis, with severe pain in the feet and knees. The serum uric acid was 16 mg. per 100 cc. He was treated with corticotropin for seven

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From the Veterans Administration Hospital, Providence, R. I.; Assistant Chief, Medical Service.

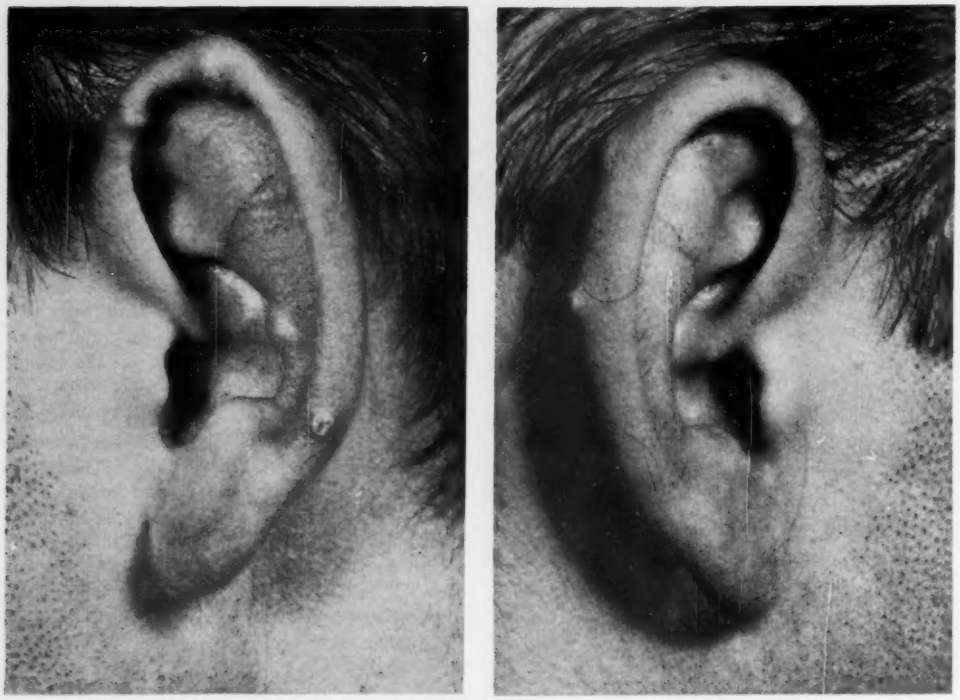

Fig. 1.—Tophi prior to probenecid therapy, in 1952.

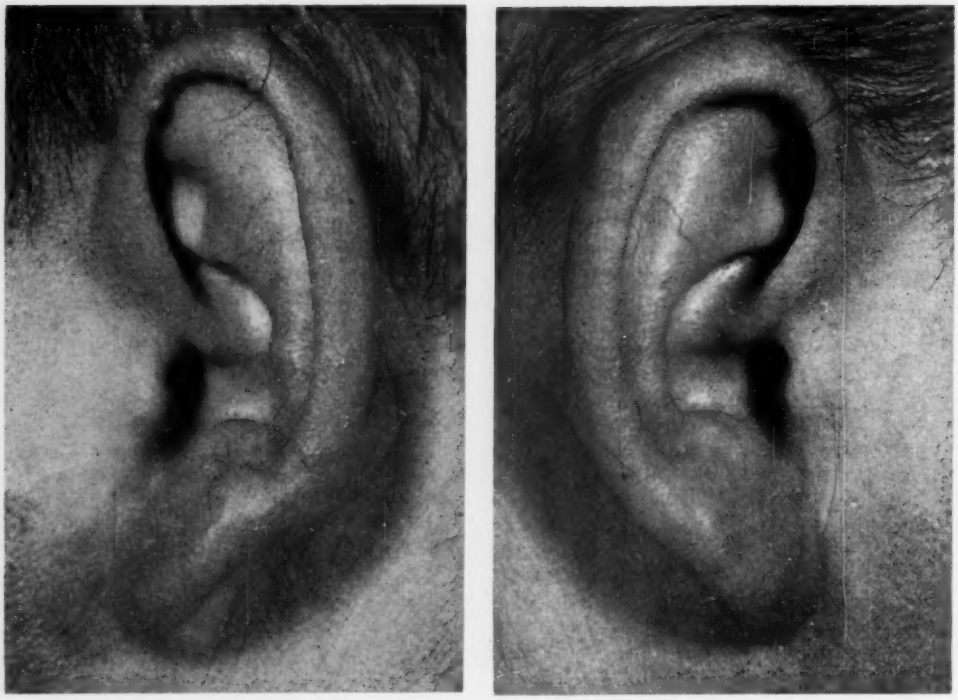

Fig. 2.—Left ear, tophi reduced in size after probenecid therapy, in 1955. Right ear, tophi disappeared after probenecid therapy, in 1955.

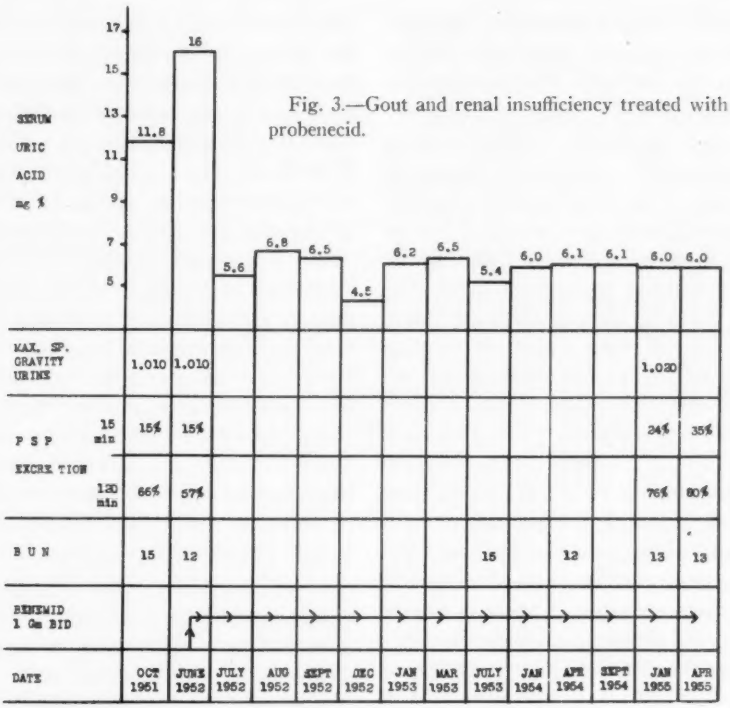

Fig. 3.—Gout and renal insufficiency treated with probenecid.

days and continued on colchicine 0.5 mg. twice daily. The acute joint pain subsided. He was then given (June, 1952) probenecid, 1 gm. daily. He also was given 5 gm. of sodium bicarbonate daily, and a high-fluid intake was advised. Colchicine was continued at maintenance dosage. On this program, the serum uric acid fell to much lower levels, where it remained (Fig. 3). The patient became symptom-free and began to gain weight. He was able to return to work one month after probenecid therapy, and has continued to work steadily up to and including the present (1955). He has had no significant joint pain. No urinary calculi have been passed, although prior to therapy with probenecid he had passed a number of them. There was a steady decrease in the size of the urate tophi and disappearance of many of them (Fig. 2). Renal-function tests have significantly improved from 1952 to 1955. PSP excretion rose from 15% to 35% in the first 15 minutes, and concentration ability increased from a maximum of 1.010 to 1.020. The urinary sediment cleared. The patient gained weight, increasing from 98 to 150 lb.

COMMENT

The inborn error of purine metabolism in gout commonly leads to elevation of the serum uric acid. The fundamental defect is not completely clear, but overproduction of urate has been demonstrated in the patient with gout.[1] Precipitation of salts of urate occurs especially in certain sites, including the bursae, articular cartilage, epiphyseal bone, ligaments, and tendons.[2] Deposits in the kidney are common,[3] and urates have been also demonstrated in blood vessels and in the endocardium.[4] A well-known favored site of tophi is the cartilage of the helix. The kidney is the principal vital organ whose function is impaired in the patient with gout.[5] The incidence of renal insufficiency is not completely known, but a considerable number of patients die from uremia. The mechanism of renal impairment has been a matter of discussion in the literature.* The types of lesions commonly found at autopsy are as follows: A. Nephrosclerosis thought secondary to hypertension and arteriosclerosis.† B. Sodium urate crystal deposits in the parenchyma of the kidney.

* References 3 and 6-10.

† References 3 and 7.

These are located in the lumen of the collecting tubules and in the interstitial tissue, primarily in the medulla. The tubular epithelium about casts of crystals is frequently destroyed and missing.‡ Tissue reaction about these deposits may show foreign-body giant cells and a few lymphocytes. Atrophy and fibrosis of tubules may be seen.§ C. Inflammatory areas of pyelonephritis may be associated with urate deposition. Acute, subacute, or chronic inflammation is seen. Interstitial fibrosis may result. It is suggested that infection may occur from obstruction of urine flow when tubules become clogged with urate crystals.‖ D. Uric acid stones may form in the renal pelvis.[2] In addition, lesions similar to glomerulonephritis have been described but these are thought to be instances of the coexistence of two separate disease entities.[10] Autopsy studies have frequently disclosed multiple types of lesions rather than a single pathologic finding.[3] Urate deposits in the kidney parenchyma have been found in all. Frequently areas of pyelonephritis have been associated with deposits of crystals. A high incidence of nephrosclerosis is also found in such kidneys. However, nephosclerosis is not universally present in gout at autopsy, even when considerable[7] renal pathology has been found. When multiple lesions occur in the kidney at autopsy, it may often be difficult to decide in terms of loss of function how much to ascribe to each lesion, or which of the lesions occurred first.

While observation of the end-stage of renal failure at autopsy is one important method of study, consideration of clinical studies in the disease also is of value, as earlier changes may be delineated indicating the primary factors involved before additional occurrences mask the original defect. This would seem to be the case in gout. The development of the picture of renal impairment is described as follows¶: The earliest evidence of renal impairment is inability of the tubules to concentrate solids maximally even though glomerular filtration is normal as judged by inulin clearance. Delayed secretion of phenolphthalein dye then occurs. Poor iodopyracet (Diodrast) visualization at pyelography is seen. As the process progresses, impairment of glomerular filtration develops and azotemia finally intervenes. The rate of progression of renal damage may be very slow. The urine as a rule shows little to no protein and few formed elements. In a series of 22 cases hypertension was not present early in the majority, even though impaired renal function was demonstrated. Later, in advanced renal failure, hypertension was present in the majority.[12] As noted, the patient described in this paper had a normal blood pressure.

The train of events suggests that the renal lesion in gout begins with tubular insufficiency. This could be due to urate deposits and/or pylonephritis or could be due to reduced blood flow to the kidney from arteriosclerosis.[12] As the disease progresses, hypertension and nephrosclerosis develop in a significant number of patients.[2] Whether this is due to nongouty heredity factors or is secondary to damage to the kidney by urate deposits has been a matter of discussion.[6] In addition, the question has been raised concerning the role of urate deposition in blood vessel walls as an etiologic mechanism of the increased incidence of vascular sclerosis seen in gout, since urate deposits in arteries have been demonstrated in relation to fibroblastic proliferation.[4]

The case presented would seem to support the concept that renal impairment in gout begins first as a result of urate deposition in the kidney. At the time the patient was studied no discernible vascular disease was found by clinical examination, although this cannot be excluded without complete pathologic study. The treatment of pyelonephritis during the patient's first admission with chloramphenicol for four days does not seem an important factor, as renal studies one year later, when probenecid was begun, had

‡ References 3 and 11.

§ References 9 and 10.

‖ References 3 and 6.

¶ References 5, 10, and 12.

remained unchanged. The improvement in renal function occurred on a program of therapy with probenecid which resulted in mobilization of urate from the tissues. Improvement in renal function on such therapy would not seem consistent with a vascular sclerotic lesion of the kidney but rather suggests that urate deposition per se in the kidney played a significant role in the pathogenesis of renal failure in this case of gout. The factors which help to clarify the problem in this patient would seem to be his relatively young age and severe disturbance of uric acid metabolism, which no doubt produced the renal picture early before it was clouded by marked degenerative vascular complications. The result of treatment in this patient indicates that at an early stage the renal lesion of gout may be reversible with therapy which results in mobilization of urate from the tissues. Further studies in gout with renal-function tests prior to and after therapy seem indicated to determine whether such findings can be consistently obtained.

SUMMARY

A case is presented of severe gout in a young man in whom reversal of renal insufficiency occurred during treatment over a 34-month period with probenecid. Marked mobilization of urate from tophi and improvement of gouty arthritis occurred in conjunction with the improvement in renal function. No clinical evidence of vascular disease was present.

The mechanism of renal impairment in gout is reviewed. Emphasis in the literature of three types of lesions is noted, namely, nephrosclerosis, urate deposits in the kidney, and pyelonephritis.

It is believed that the improvement in renal function favors the concept that the impairment in kidney function in gout began first in this case as a result of urate deposition.

The renal lesion of gout may be reversible with treatment with probenecid in early stages before secondary degenerative vascular lesions of the kidney occur.

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PLASMA-CELL MYELOMATOSIS

Report of a Case with Multiple Large Tumors Involving the Digits of Both Hands

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THE INFREQUENT occurrence of involvement of the small bones of the hands and feet in multiple myeloma has often been referred to or implied in the description of skeletal involvement in this disease.* Lichtenstein and Jaffe [3] indicated that occasionally a bone of the foot or hand may be the site of the presenting lesion. Meyerding [4] in 1925 presented a case with diffuse involvement in the bones of the hands, as shown by roentgenograms.

This case is presented because of the occurrence of multiple large tumors involving the digits of the hands, which represented the initial symptoms of the disease, and which led to its diagnosis by way of aspiration biopsy.

REPORT OF CASE

A 57-year-old white man, a streetcar motorman, was admitted to the hospital on June 18, 1953, with the complaint of painful swelling of the distal portion of the middle finger, right hand, of six weeks' duration. Two days prior to admission the patient noted swelling of the fifth finger, right hand, and the index finger of the left hand.

The patient had been essentially well until about three years previously, when he developed a fever and difficulty in breathing. He was told he had a heart attack and was hospitalized for several weeks. He managed fairly well until one year prior to admission, when he noted shortness of breath on exertion. This persisted for several months and was associated with slight swelling of the feet and ankles toward the end of the day. With the shortness of breath on exertion there was substernal distress and discomfort. In December, 1952, the patient developed a cold with a cough, and he was hospitalized in January, 1953, when an electrocardiogram showed a "bad heart." In March, 1953, the patient returned to work but developed left posterior chest pain that was aggravated by deep breathing. This disappeared on antibiotic therapy.

About six weeks prior to admission the patient noted swelling of the distal phalanx of the middle finger, left hand, associated with a throbbing pain. The swelling increased to walnut size during the next four weeks. After the left middle finger began to swell, the start of swelling was noted in the right middle finger similar in character to that of the one previously involved. About this time he noted some pain in the right knee and right ankle when walking. The patient consulted his physician, who treated him for congestive failure with digitoxin, diuretics, and sodium restriction, under which therapy his breathing difficulty improved. The swelling of the distal end of the left middle finger was incised and drained, and a dark bloody material was obtained. The patient was then given antibiotic therapy. He developed urticaria, which progressed to such a degree that he was treated for about 20 days with cortisone. In this period the finger of the right hand continued to enlarge. About one week after the finger was drained he noted a "bump" on his forehead, just to the right of the midline, which was about 3 cm. in diameter and elevated about 1 cm. It was nontender, firm, and rubbery. This swelling remained for about three to four weeks and then gradually disappeared, leaving a depression in this same area.

The patient states that he had lost 10 lb. in the six weeks prior to admission. There were no other complaints referable to the other systems. The family history revealed that one sister died of leukemia. His father died of carcinoma of the liver. The paternal grandfather died of carcinoma, site unknown. A paternal uncle died of carcinoma of the stomach.

Physical Examination.—The patient was a well-developed, well-nourished moderately obese white man who appeared chronically ill. Examination of the head revealed an area of depression over the

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From the VA Hospital.
* References 1 and 2.

Fig. 1.—Appearance of hands on admission, showing tumors of left second and right third and fifth digits.

right side of the forehead measuring 1×2 cm. A similar but smaller depression was noted on the left. There was no distention of the cervical veins. The anteroposterior diameter of the chest was increased, and a few crepitant rales were heard in the right base, posteriorly. There was no dullness, and breath sounds were heard throughout. The heart was enlarged to the left on percussion. The rhythm was regular, and tones were distant, but no murmurs were heard. The blood pressure was 122/80. The abdomen was obese. The liver was felt 3 to 4 cm. below the right costal margin and was tender. The spleen was enlarged 3 to 4 cm. below the left costal margin. No other organs or masses were felt. Neurological examination revealed normal findings. There was no lymphadenopathy. The left hand showed a diffuse, rather firm swelling in the index finger involving the area of the entire middle phalanx. The skin showed brownish discoloration. The distal phalanx of the middle finger revealed a healed scar on the lateral aspect and displayed increased mobility. On the right hand there was a large cyst-like mass which was rubbery, involving mainly the area of the middle phalanx of the middle finger. The skin overlying the mass was bluish, with increased pigmentation. The right fifth finger presented a

Fig. 2.—Extensive osteolytic lesions in the fingers of both hands (hands have been reversed [left for right] from preceding Figure).

Fig. 3.—Radiolucent areas in the skull.

Fig. 4.—Osteolytic lesions in the metatarsals.

fusiform, rather firm swelling involving the middle and distal phalanges. A 2+ pitting edema was present in the legs, with pain on extension of the right knee. Tenderness was present over the superior lateral area of the right knee.

Laboratory Data.—The initial urinalysis revealed a specific gravity of 1.004, with the remainder of the examination being negative. Throughout his hospital stay the specific gravity ranged from 1.004 to 1.012, with only a trace and a faint trace of albumin noted on two occasions. The admission red blood cell count was 4,290,000, with a hemoglobin of 13 gm. There were 8000 white blood cells, with 57% neutrophiles, 43% lymphocytes, and a sedimentation rate of 21 mm. in an hour. The red cell count has varied only slightly, and the last determination revealed 4,400,000, with a total white cell count of 5400, with 55% neutrophiles and 45% lymphocytes. Hemoglobin again was 13 gm. and sedimentation rate was 9 mm. in an hour. Serological studies were negative. On admission the blood urea nitrogen was 13.9 mg. per 100 cc.; uric acid, 4.3 mg. per 100 cc.; total protein, 6.2 gm., with 3.7 gm. albumin and 2.5 gm. globulin per 100 cc. Blood sugar was 93 mg. per 100 cc. Total protein has ranged from 5.9 to 7.2 gm., but the albumin-globulin ratio has been normal. Blood

Fig. 5.—Aspiration biopsy specimen of right third finger, showing characteristic plasma cells.

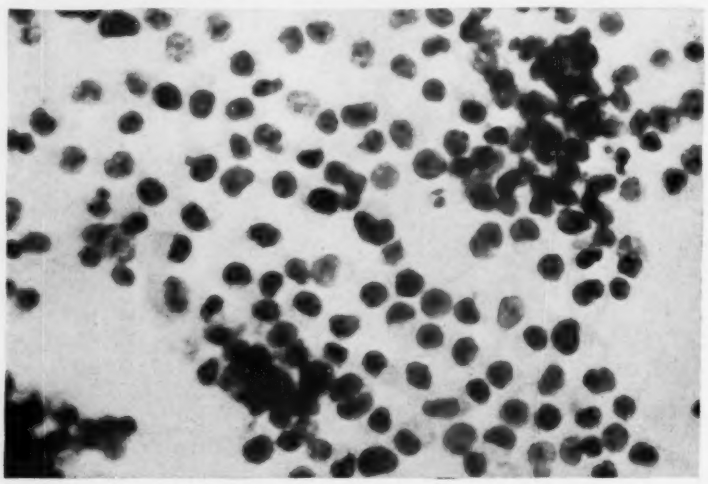
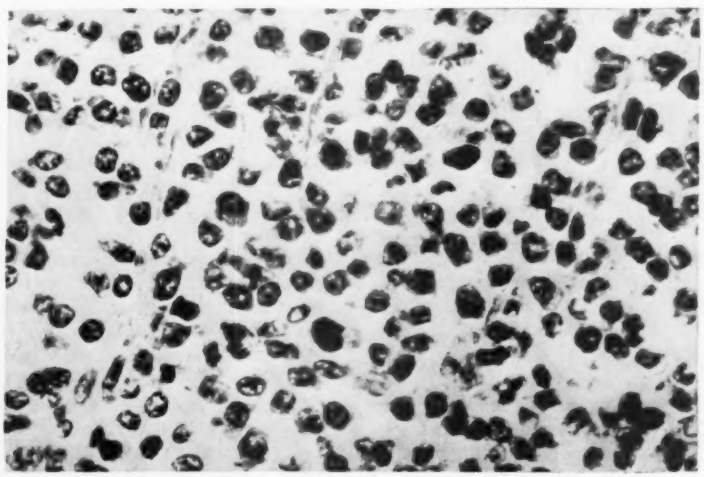


Fig. 6.—Surgical specimen, showing extensive destruction of the middle phalanx, with replacement by tumor mass.

cholesterol was 234 mg. per 100 cc. on admission. On June 29, 1953, the alkaline phosphatase was 3.8 Bodansky units and ranged between 2.8 and 4.6 units until, on Jan. 11, 1954, it was 3.3 Bodansky units. Acid phosphatase was normal. On July 6, 1953, the serum calcium was 10.3 mg. per 100 cc.; the serum inorganic phosphorus, 3.1 mg. per 100 cc. On Aug. 3, 1953, the calcium was 11.3 mg. per 100 cc. Repeated examinations of the urine for Bence Jones protein were negative. X-ray examination of the chest revealed approximately 20% cardiac enlargement. X-ray examinations of the skeleton revealed numerous osteolytic areas in the skull. Punched-out lesions were noted at the distal end of the right femur and in the shaft of the left femur. There was almost complete destruction of the middle phalanx of the right third digit, with destructive lesions in the middle and distal phalanges of the right fifth digit and middle phalanx of the second finger and complete destruction of the distal phalanx of the third left digit. X-rays of the feet revealed destructive lesions in the shaft of the left first metatarsal, right first metatarsal, distal end of the right second metatarsal, distal head of the left fifth metatarsal, and the posterior inferior portion of the right os calcis. A destructive lesion was noted in the left wing of the ilium and the distal end of the left tibia, and an osteolytic lesion was also noted in the left scapula. There was compression of T11. X-ray of the ribs and intravenous pyelogram revealed no abnormality. An electrocardiogram showed a left bundle branch block.

Hospital Course.—The patient was admitted to the hospital on June 18, 1953. He was treated at that time for congestive failure, which relieved his shortness of breath and ankle edema. An aspiration of the tumor mass of the right middle finger was accomplished on July 6, 1953, this same finger being amputated on July 14, 1953. Deep x-ray therapy was instituted to the left second finger and the medial malleolus of the right ankle anteriorly, which gave the patient slight symptomatic relief. About July 31, 1953, he developed pain in the back, and a prominence of the dorsal spine of the 11th thoracic vertebra was noted. The patient's general state has remained fairly stable except that he is limited in his activity because of back pain and is unable to walk because of pain in his ankles. While in the hospital the patient has been afebrile except for the first week of his hospital stay, when a low-grade fever, with temperature up to 99.8 F, was present.

Fig. 7.—Section of tumor tissue from surgical specimen.



Pathology.—A bone marrow aspiration on June 2, 1953, revealed hyperactive bone marrow of the granulocytic type with increased number of eosinophiles. It was interpreted as being nonspecific. A repeat bone marrow study, on March 3, 1954, showed a cellular bone marrow with adequate numbers of megakaryocytes and myeloid and erythroid elements. There was an increase in the number of plasma cells over that seen in the previous marrow. A diagnosis of multiple myeloma could not be made on the basis of this marrow specimen, and it also was interpreted as nonspecific. Aspiration of the tumor mass of the right middle finger on July 6, 1953, revealed cells that had a pink cytoplasm and darkly stained eccentrically placed nuclei. Some of the cells displayed a cartwheel appearance of the chromatin, while others showed mitotic figures. The surgical specimen consisted of the left middle finger, the proximal two-thirds of the substance being completely replaced by a gray soft tumor mass, involving the middle phalanx, with almost complete destruction of the bone in this area. Microsection showed the skin along the surface to be covered by a normal stratified squamous epithelium. Underlying it there was a large solid mass of cellular elements with very little supporting stroma. The tumor mass broke through the tissue planes in an insidious manner and infiltrated the surrounding tissue. There were occasional multinucleated cells with a clear space about the nucleus.

COMMENT

Most reviews analyzing the skeletal lesion in multiple myeloma indicate the infrequency of involvement of the bones of the hands and feet. This case has been of considerable interest to us in that the patient (1) presented with large tumors involving the digits of both hands and (2) has shown extensive skeletal involvement roentgenographically in spite of failure to demonstrate the classical features of multiple myeloma. The patient has shown no anemia, Bence Jones proteinuria, nor any electrophoretic abnormality typical of the disease. There have been no myeloma cells demonstrated in the marrow during nine months of continuous hospital observation. Although there has been compression fracture of a vertebral body (T11), the patient's general physical state has shown no remarkable deterioration during his hospital course.

The observations made in this case introduce some speculation as to the natural course of the disease. One might expect to find myeloma cells in the marrow and anemia in a case with such diffuse skeletal involvement. Yet this case does not show remarkable osteoporosis, as would be expected in a diffuse marrow involvement. Snapper[5] describes multiple plasmacytomas wherein there is not generalized myelomatous involvement of the marrow and without Bence Jones proteinuria or remarkable changes in serum proteins. He states that such cases are rare. On the other hand, this case may represent but a stage of the disease which will eventually be characterized by the typical changes noted above.

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Correspondence

SICKLE CELL TRAIT AND DISEASE IN PULMONARY TUBERCULOSIS

To the Editor:—The April issue of the A. M. A. Archives of Internal Medicine contains a paper by Rosenblum et al. on the lack of relationship between the sickle cell trait and tuberculosis in Negroes. Reference is made to our previous publication (Weiss, W., and Stecher, W.: Tuberculosis and the Sickle Cell Trait, A. M. A. Arch. Int. Med. **89**:914-922 [June] 1952) with the implication that the results of our investigation have not been confirmed. Therefore I would like to take this opportunity to point out several considerable and significant differences between our work and the investigation of Rosenblum et al.

We reported that the sickle cell trait is more than twice as common (12.6%) among tuberculous Negroes admitted to a large municipal general hospital as it is among nontuberculous Negroes admitted to the same hospital (5.3%). We would like to emphasize that we had a control series, that all the individuals in both series were hospitalized patients, that the study of both series was concurrent, and that all persons in the control series had a negative chest photofluorogram because we eliminated those who had pulmonary disease. These criteria for the selection of patient material were not followed by Rosenblum et al. and their investigation is therefore not comparable to ours.

The technic of the metabisulfite test for sickle cells deserves some mention. Rosenblum et al. read their sickle cell preparations in a rather short time. The technic as described by Daland and Castle (Daland, G. A., and Castle, W. B.: A Simple and Rapid Method for Demonstrating Sickling of the Red Blood Cells: The Use of Reducing Agents, *J. Lab. & Clin. Med.* **33**:1082 [Sept.] 1948) involves reading the test after 3.5 hours, and we found that occasionally a preparation may not show sickle cells for several hours.

Our second conclusion was that exudative tuberculosis is twice as common among tuberculous Negroes with the sickle cell trait (74%) as it is among tuberculous Negroes without the trait (38%). The term "exudative tuberculosis" was clearly defined and illustrated with roentgenograms. Rosenblum et al. compared these two groups of tuberculous Negroes only with respect to the extent of disease in the lungs and made no mention of the type of tuberculosis.

Our third conclusion was that the sickle cell trait has definite clinical significance and is a factor in the response of some Negroes to tuberculous infection. Of course, since the sickle cell trait in the United States is found in only a small segment of the Negro population; it likewise has clinical significance in only a small segment of the tuberculous Negro population. Nevertheless it is of interest and in the last few years more and more papers have appeared in the literature ascribing clinical importance to the sickle cell trait under certain conditions such as the hypoxia of high altitude flight (Smith, E. W., and Conley, C. L.: Sicklemia and Infarction of the Spleen During Aerial Flight, *Bull. Johns Hopkins Hosp.* **96**:35-41 [Jan.] 1955). Evidence has been presented that the sickle cell trait affords protection against malaria (Allison, A. C.: Protection Afforded by Sickle Cell Trait Against Subtertian Malarial Infection, *Brit. M. J.* **1**:290 [Feb. 6] 1954). In addition there have been accumulating reports of cases of sudden death and various disease states secondary to disturbed blood supply associated with the sickle cell trait. Thus it will be necessary in the future to revise those textbooks which continue to state that the sickle cell trait has no clinical significance.

William Weiss, M.D.
Philadelphia.

To the Editor:—Dr. Weiss reported "that sickle cell trait is more than twice as common (12.6%) among tuberculous Negroes admitted to a large municipal general hospital than it is among nontuberculous Negroes admitted to the same hospital (5.3%)" and stressed the importance of his control series studied concurrently with the observed cases as well as the negative chest photofluorogram in control series.

At Kings County Hospital, where the hematology division has been actively studying sickle cell anemia since 1946, we have repeatedly demonstrated the rather constant incidence of about 8% of persons with sickleable cells. An early report from this hospital is that of Watson, J.; Stahman, A. W., and Bilelle, F. P.: *Am. J. M. Sc.* **215**:419, 1949, which included 226 con-

secutive Negro females with a sickling incidence of 8%. More recently, since the introduction of the filter paper electrophoresis technique, we have screened large numbers of Negroes of both sexes in this hospital and once again noted an incidence close to 8%. X-ray examination of the chest is routine on the medical wards.

As for the technique of demonstrating sickleable cells by use of the metabisulfite test, we are convinced of the validity of our interpretations. We know from carefully controlled experiments performed for other purposes than the present report that the maximal sickling of cells may not occur within one hour only in rare instances. The great majority of cells capable of sickling, however, will be sickled in that period of time. In the present study, if any sickled cells were found, no matter how few, the patient was tentatively classified as having the sickle cell trait and the blood was then subjected to filter paper electrophoresis for confirmation.

Dr. Weiss objects to the fact that our study discussed the extent of pulmonary tuberculosis, rather than exudative or fibrotic. On this point it is sufficient to state that all of our tuberculous patients are predominantly exudative and all are active cases. Our classification was based on the Diagnostic Standards and Classification of Tuberculosis, National Tuberculosis Association, 1950. The extent of the disease is more significant in estimating the progress of the disease and the immunity of the body to tuberculosis. Also, there have been reported studies of the inherent errors and wide variation, even in the same reader at different times, in the radiologic interpretation of chest roentgenograms, which would argue against the classification used by Dr. Weiss.

There certainly is a great interest at present in the question of whether or not sickle cell trait has any clinical significance. We are inclined to believe that it probably does, under certain circumstances, i. e., in the presence of malarial vectors, high altitude flying, and severe anoxia. Our studies in tuberculosis, however, indicate that this disease may not be one of those circumstances. Our experience has further shown that patients with sickle cell trait can be made ill by pulmonary conditions producing hypoxemia. But this logically demonstrates that sickle cell trait may be affected by a superimposed condition but not the converse, as Dr. Weiss wishes us to believe.

It is gratifying, nevertheless, to be able to read the comments of Dr. Weiss.

HAROLD A. LYONS, M.D.
New York.

News and Comment

ANNOUNCEMENTS

Symposium on Cancer Research.—The Tenth Annual Symposium on Fundamental Cancer Research will be held on March 29, 30, and 31, at The University of Texas M. D. Anderson Hospital and Tumor Institute in the Texas Medical Center, Houston.

A panel discussion on nucleic acid metabolism in tumors will be under the direction of Dr. Van R. Potter, professor of oncology at the University of Wisconsin Medical School. Dr. Darrell Ward, department of biochemistry, M. D. Anderson Hospital, is in charge of the reports on recent developments in cancer research. Dr. Grant Taylor, Dean of The University of Texas Postgraduate School of Medicine, is general chairman of the Symposium.

Fourth International Congress on Diseases of the Chest.—The American College of Chest Physicians, an international society, has announced that its Fourth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the College, will be held in Cologne, Germany, Aug. 19 through 23, 1956.

Chancellor Konrad Adenauer is the Honorary President of the Congress, and one of Germany's most famous scientists, Dr. Gerhard Domagk, who received the Nobel Prize for his discovery of the sulfonamides, is President. Other officers are Prof. H. W. Knipping, of Cologne, Vice President, and Prof. Josef Jacobi, of Hamburg, Secretary General. The Executive Committee in charge of arrangements for the Congress has as its chairman Prof. Joachim Hein, of Schleswig-Holstein, Regent of the College for Germany.

The scientific program to be presented at the Congress is now being organized, and physicians having carried out original work in diseases of the chest (heart and lungs) which they wish to present are invited to send outlines of their studies to Dr. Andrew L. Banyai, Chairman, Committee on Scientific Program, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11. Physicians who have motion pictures or exhibits dealing with heart and lung disease are also requested to submit complete data to the committee. All requests for places on the scientific program will be given due consideration.

The Hon. Ernest Schwering, Mayor of Cologne, extends a cordial invitation to physicians and surgeons throughout the world to attend this congress on chest diseases. Further information may be obtained by writing to the Executive Offices, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

American Board of Nutrition Examinations.—The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition, in April, 1956. Applications for certification should be in the office of the Secretary not later than Feb. 1, 1956. Application forms may be obtained, on request, from the Secretary, Otto A. Bessey, Department of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Texas.

Books

EDITED BY WILLIAM B. BEAN, M.D.

Pediatric Diagnosis. By Morris Green, M.D., and Julius B. Richmond, M.D. Price, $10.00. Pp. 436. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

This volume on pediatric diagnosis is arranged for use as a short, ready reference. The first chapter, which is entitled "The Pediatric History," suggests that the history should be chiefly in the nature of an interview for the purpose of eliciting evidence of disturbed psychologic or psychiatric status. It might have been better had it been inserted later in the volume as a set of remarks bearing on the psychosomatic aspects of pediatrics. The authors approach differential diagnosis on the basis, first, of physical findings and, secondly, of signs or symptoms. Systematic examination of the anatomic parts and organs of the body is suggested to reveal important abnormalities, developmental disturbances, and acquired pathologic states.

Emphasis is placed on the more recently recognized importance of growth and development as well as on psychic factors and disturbances, and these receive special treatment in several sections.

The insertion of references immediately after the statements to which such references are related should be found helpful. For the most part, the specific references, as well as the general references included at the ends of the various sections, represent contributions which are recent and which originate in reliable sources.

The table of contents, the index (which is too limited to be of great value), and the cross references in the text permit access to the material that is available.

As the authors indicate, the treatise is not exhaustive but may be of help to undergraduate students and general practitioners.

The volume is without illustrations, but the authors have succeeded in drawing some good word pictures where visual understanding is required.

Subsequent revisions will probably afford an opportunity to eliminate the typographical errors.

A Textbook of Physiology. Edited by John F. Fulton, M.D., Sterling Professor of the History of Medicine, Yale University School of Medicine. Seventeenth edition. Price, $13.50. Pp. 1275, with 600 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1955.

The seventeenth edition is a complete revision of Howell's "Textbook of Physiology," now edited by Dr. John F. Fulton. The problem of covering the recent advances in the field of physiology has been admirably solved by the selection of qualified contributors for the various chapters. The paper, print, cuts, and drawings are excellent, the arrangement of the references at the end of each chapter is complete and most helpful to the reader.

There appear to be two criticisms of this excellent textbook. It seems that so many details of neurophysiology are stressed that other important systems, such as the gastrointestinal tract, are left wanting in a full discussion of their physiology. Some improvement could also be made if the book had covered, in an organized small chapter, the basic facts on the physiology of the various constituents of the connective tissue. There seems to be a rather urgent need for some information on the physiology of connective tissue as a basis for the understanding of the fundamental changes in the diseases recently classified under the heading "diseases of collagen."

However, this book can be highly recommended to medical students and practitioners who are interested in keeping abreast of the recent trends in physiology. The editor and the contributors are to be congratulated for having collaborated admirably in preventing unnecessary overlap in the discussion of the various subjects and for having contributed jointly to make the book a valuable source of information in the enormous field encompassed by today's physiology.

Annual Review of Physiology: Volume 17. Edited by Victor E. Hall, M.D. Price, $7.00. Pp. 551, with 1 illustration. Annual Reviews, Inc., and the American Physiological Society, Stanford, Calif., 1955.

This, the 17th volume in what is established as a very important series, continues the standards set by its predecessors. Its virtue is that is covers a wide field but varies somewhat from year to year. Thus it reflects the regions in physiology of most intense interest and activity.

As such, it serves as to cover the middle ground between the exhaustive critical monograph and a sparsely annotated bibliography presenting brief comments on much new work. In addition, some effort is made in the direction of critical evaluation. To those beset by the problem of trying to keep up with areas of research other than their own field, such as a physician has in following what is going on in physiology, the study of books such as this offer the nearest approach to a solution. It is a pity that the delightful autobiographical reflections of Frank C. Mann have, as page one, the stark disclaimer of responsibility and belief expressed by the editorial board.

Tumors of Lymphoid Tissue. By George Lumb, M.D. Price, $8.00. Pp. 204, with 182 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Tevoit Place, Edinburgh 1; Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

"Tumors of Lymphoid Tissue" is a two-hundred-page monograph based on the study of 410 patients with lymphoma from Westminster Hospital and Westminster Medical School, London University.

The text opens with a brief survey of the structure, function, and significance of lymphoid tissue and is followed by an historical survey of the subject. From here the author proceeds to terminology and classification and outlines his own classification of lymphomas based on morphology and cytogenesis. This classification places the lymphomas in the following four major categories: I. those characterized by primarily lymphocytic proliferation (follicular lymphoma and lymphosarcoma), II. those characterized by reticulum-cell proliferation (reticulum-cell sarcoma), III. those characterized by mixed cell proliferation (Hodgkin's disease and "reticular lymphoma"), and IV. anaplastic sarcoma, including anaplastic variants of all groups. The term "reticular lymphoma" is applied to the unusually benign type of Hodgkin's lymphoma which was described and called "early Hodgkin's" or "Hodgkin's paragranuloma" by Jackson and Parker.

Each of these entities is discussed briefly in terms of incidence; anatomical distribution, presenting symptoms, and natural history of the disease; gross and microscopic pathology, and differential diagnosis. The material presented is generously illustrated with photographs and low- and high-power photomicrographs. A detailed chapter on problems of diagnosis discusses important details of the choice of lymph node biopsy, fixation, and staining and reviews the problem in diagnosis presented by the specific and nonspecific inflammatory reactions of lymphoid tissue. A brief specific discussion of the effects of various forms of therapy on these tumors is followed by a summary of the whole problem and a chapter of case presentations of representative clinical cases.

This presentation is short and well organized. The author's classification of the lymphoid tumors is logical, although the invocation of the term "reticular lymphoma" is likely to be confusing to those unfamiliar with this specific application to the benign type of Hodgkin's disease. The author distinguishes the histological features of reticulum-cell sarcoma of bone from the reticulum-cell sarcoma of lymphoid tissues, but he fails to indicate any difference in the clinical course or prognosis. In this classification, the category of anaplastic sarcoma includes anaplastic variants of all the lymphomas, most of which are anaplastic lymphoblastomas and Hodgkin's sarcomas. The composition of this last category is one which clinicians may consider arbitrary and illogical, since many previously well-defined lymphomas may become anaplastic as the disease progresses.

Despite the fact that this treatise is naturally slanted to the viewpoint of the pathologist and is based on a comparatively small series of cases, it represents a fair appraisal of the problem and presents a sound and brief discussion of the morphological and clinical features of each type of lymphoid tumor. The monograph can be well recommended to anyone interested in oncology, but it seems best suited to the needs of the internist and general surgeon who has a practical interest in the lymphomas.

Peripheral Nerve Injuries. Edited by H. J. Seddon. Price, not given. Pp. 451. Her Majesty's Stationery Office, York House, Kingsway, London, W. C. 2, 1954.

Every major war brings with it a renewed interest in and a better understanding of the peripheral nerves, the results of their injury and the most appropriate forms of treatment. Our own Civil War contributed Weir Mitchell's classic studies of causalgia. The first World War brought a much better understanding of the surgical treatment of injuries of the peripheral nerves and the brilliant experimental studies of Carl G. Huber (whose work is referred to but once, and the very briefly, in this monograph). World War II taught us much and also brought forth many ideas which were tried, found wanting, and completely or largely

discarded. Most outstanding of the many additions to our knowledge are the value of sympathectomy in the treatment of causalgia, the importance of early surgical repair, the dangers of prolonged immobilization and inactivity.

Although there have been many shorter, individual publications in this field during and since the War, this monograph represents the over-all survey of the studies which were made by the British during this period. (A similar thoroughgoing report by the Americans is soon to be published.) This report has been prepared by a group of twelve British scientists and clinicians. "No attempt has been made to present a systematic account of the diagnosis and treatment of nerve injuries"; instead, this report is concerned "only with advances in the understanding of nerve injuries made by British workers during the war years."

The first chapter, by H. J. Seddon, is concerned with methods of investigation. Among the more important matters considered here are the varying and anomalous muscular and sensory innervation of the peripheral nerves. It is also interesting to find Tinel's sign, long discarded as worthless or misleading, again restored to a position of some value.

The second chapter is by Ruth E. M. Bowden and D. A. Sholl and is principally of interest in showing the great variation of rates of regeneration of different nerves under varying circumstances.

The third chapter, on vasomotor and nutritional disturbances, is by R. L. Richards. The next chapter, by R. B. Zachary and R. Roaf, deals with lesions in continuity. It is thorough and stimulating. The authors conclude that where there is evidence of injury to a peripheral nerve "exploration is seldom, if ever, regretted but neglect of it frequently has serious consequences." This is one of the most important lessons taught by this catastrophic experience. The next section, on nerve injuries and fractures, is by D. M. Brooks, and the next, on the histopathology of nerve injury, is by W. Blackwood and W. Holmes. The section on the histopathology of nerve grafts, by F. K. Sanders, emphasizes that only autogenous grafts offer any prospect of success. Grafts of nerves fixed in alcohol or formulin result only in failure. Most of this chapter is given over to experimental observations on animals, with a disappointingly brief section on human material. In the chapter on causalgia R. Barnes is very positive that "sympathectomy is the only form of therapy likely to be effective" in the severe forms of this distressing condition. His results were better in the lower than in the upper extremities, and he found that preganglionic section gave better results than ganglionectomy. The author was unable to clarify the etiology of this puzzling condition. R. L. Richardson discusses the simultaneous occurrence of injury to the peripheral nerves and the vascular system and feels that the presence of the neurological lesion will seldom influence the type of treatment required by an aneurysm or an arteriovenous fistula. It is also his opinion that the association of the two lesions does not worsen the prognosis. The sections on electrical diagnosis by, A. E. Ritchie, and electromyography, by Ruth E. M. Bowden, show that these are detailed time-consuming techniques which are of greater research than clinical value. The chapter on factors influencing functional recovery, by Ruth E. M. Bowden, is one of the most extensive in the book. She emphasizes the importance of proper splinting with avoidance of immobilization beyond that required for healing of wounds and fractures and firm union of sutured nerves. She devotes considerable space to various types of splints and to the importance of exercise and the early mobilization of joints. Electrotherapy has not been shown to have any great usefulness. R. B. Zachary discusses the results of nerve suture, and H. J. Seddon, those of nerve grafts in great detail and with many tables.

In the concluding chapter, D. M. Brooks discusses wounds of the brachial plexus and concludes that surgical repair and exploration in such cases is not worth while.

There is an extensive bibliography and a thorough index.

The value of this book to everyone interested in the problems resulting from injuries to the peripheral nerves is obvious.

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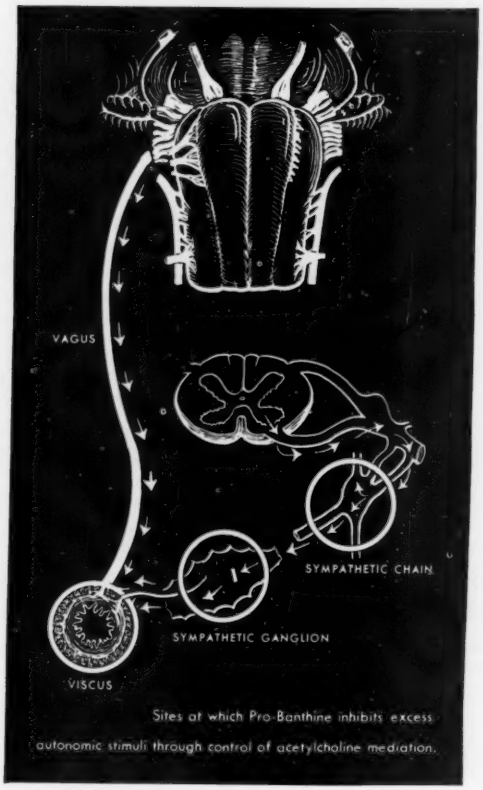

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

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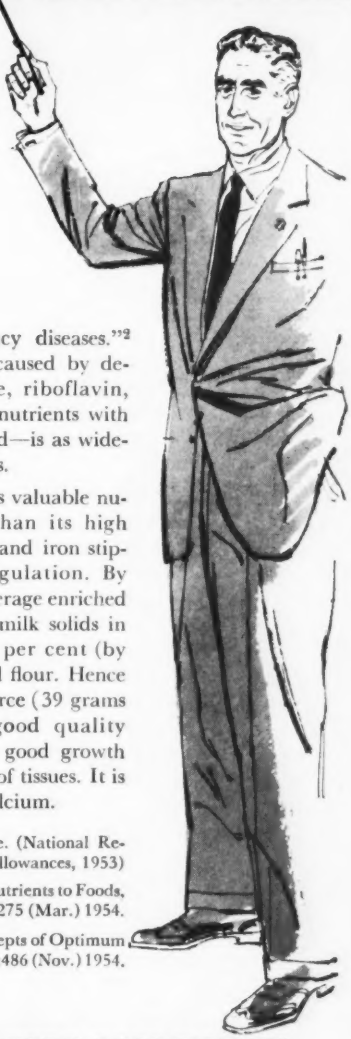

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1. The Addition of Specific Nutrients to Foods, Public Health Reports *69*:275 (Mar.) 1954.

2. King, C. G.: Newer Concepts of Optimum Nutrition, Food Technol. *8*:486 (Nov.) 1954.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

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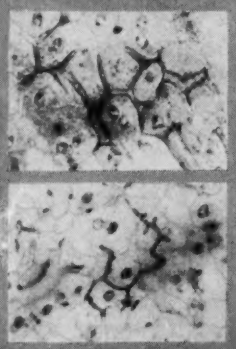

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(1) Clara, M.: Med. Monatsschr. *7*:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

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